Paid Circulation, 37,262

A. M. A. CLINICAL MEETING
Boston
November 29-December 2, 1955

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 253 • NOVEMBER 3, 1955 • NUMBER 18

Original Articles

Advances in the Diagnosis of Altered States of Adrenocortical Function 747
John C. Laidlaw, William J. Reddy, Dalton Jenkins, Najib Abu Haydar, Albert E. Renold and George W. Thorn

Blood Levels from Orally Administered Penicillins G and V: Relation to Food Intake 754
Wilfred F. Jones, Jr., and Maxwell Finland

Salmonellosis Originating in a Hospital: A Newly Recognized Source of Infection . 761
Lawrence J. Kunz and Orjan T. G. Ouchterlony

Alevaire as a Mucolytic Agent 764
Maurice L. Tainter, Frederick C. Nachod and Joseph G. Bird

Special Article

School Health and the Family Physician . . 767
Kenneth L. Maclachlan

Medical Progress

Treatment of Migraine (To be concluded) . . 770
John R. Graham

Medical Intelligence

Local Tetanus: Report of a Case Involving the Left Facial Muscles 777
E. Converse Peirce, II, and C. Harwell Dabbs

Doctors Afield: Imhotep 778
William H. Sprunt

Case Records of the Massachusetts General Hospital . . 780

Editorials

Oral Administration of Penicillin 789
Red Feather Campaign 790
Poliomyelitis Vaccine Program Deferred . . 790
T. Duckett Jones Memorial Fund 791

Massachusetts Medical Society 791
Notices 793
Correspondence 792

THE MODERN, POWERFUL HEMATINIC

'Trinsicon'

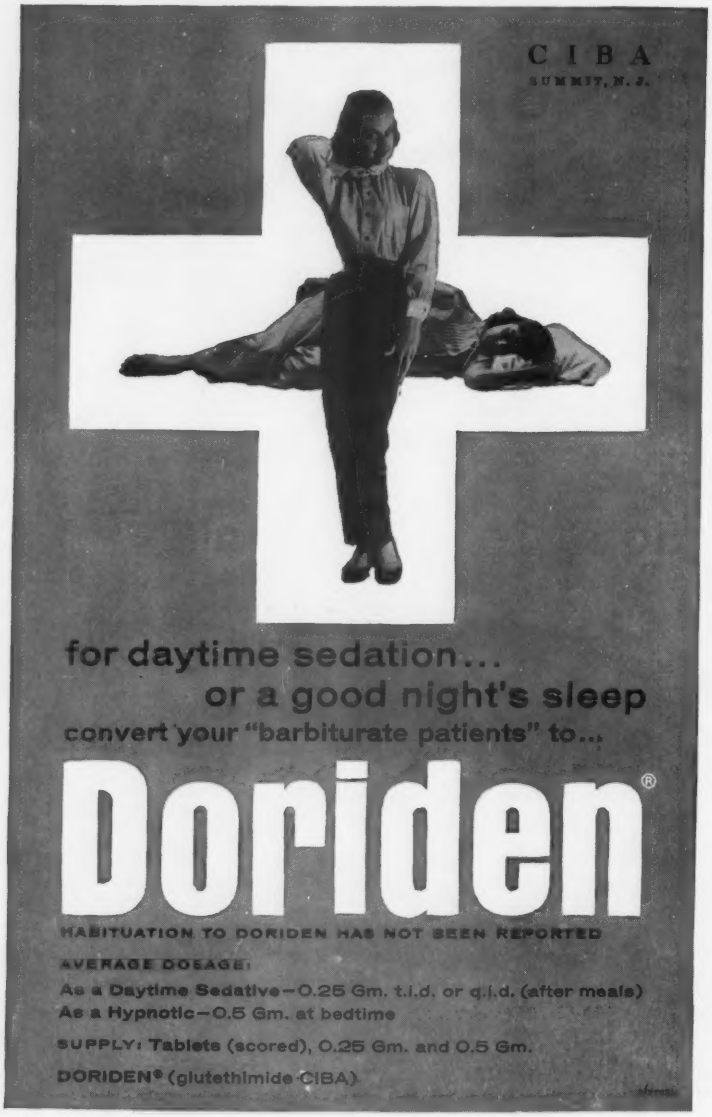
(HEMATINIC CONCENTRATE WITH INTRINSIC FACTOR, LILLY)

POTENT • CONVENIENT • ECONOMICAL

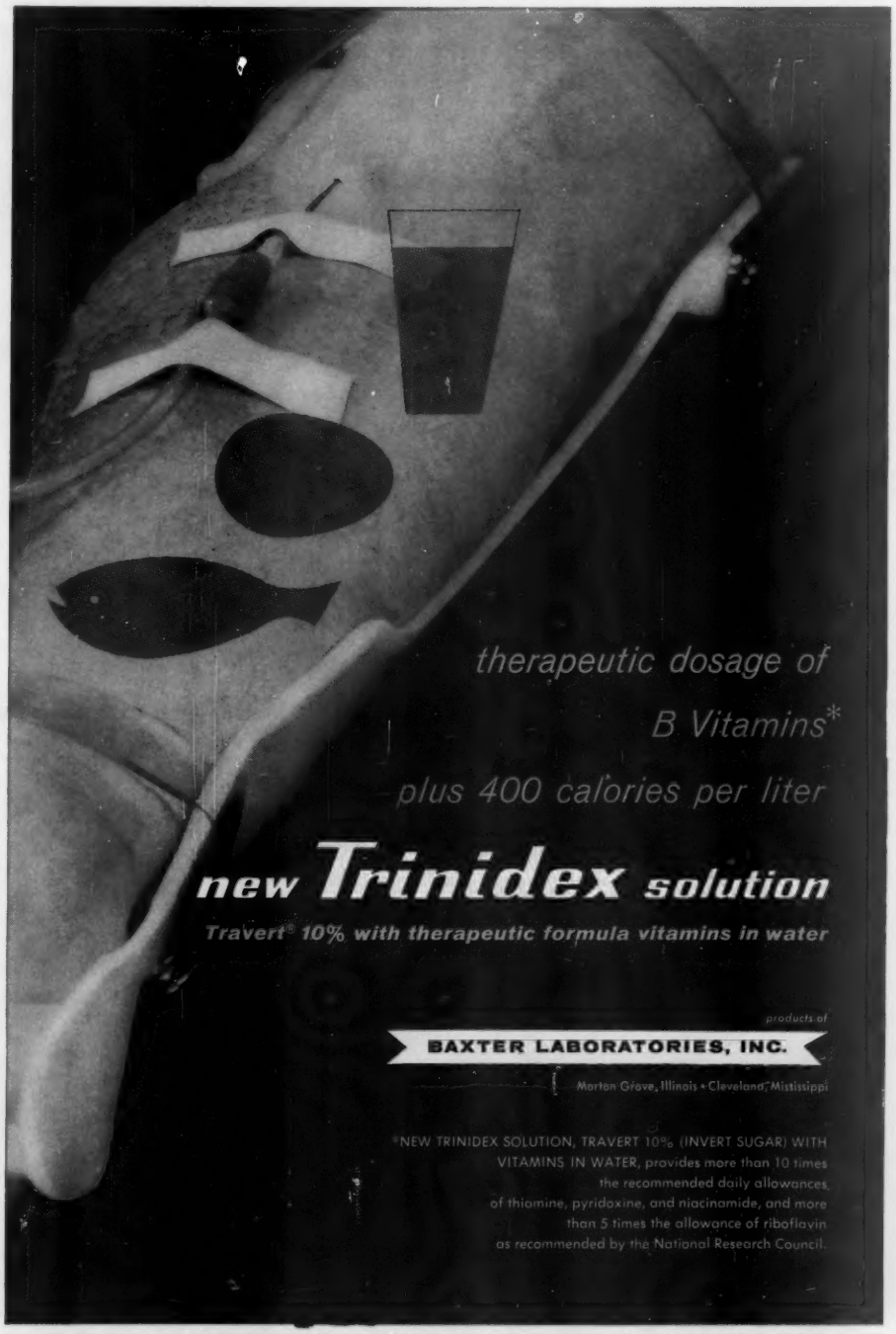
2 a day for all treatable anemias

Lilly

In bottles of 60 and 500 pulvules.


CIBA
SUMMIT, N. J.
for daytime sedation...
or a good night's sleep
convert your "barbiturate patients" to...
Doriden®
HABITUATION TO DORIDEN HAS NOT BEEN REPORTED
AVERAGE DOSAGE:
As a Daytime Sedative—0.25 Gm. t.i.d. or q.i.d. (after meals)
As a Hypnotic—0.5 Gm. at bedtime
SUPPLY: Tablets (scored), 0.25 Gm. and 0.5 Gm.
DORIDEN® (glutethimide CIBA)

MEDICAL HORIZONS TV Monday P.M. *Sponsored by* CIBA ABC-TV


therapeutic dosage of
B Vitamins*
plus 400 calories per liter
new Trinidex solution
Travert® 10% with therapeutic formula vitamins in water
products of
BAXTER LABORATORIES, INC.
Morton Grove, Illinois • Cleveland, Mississippi
*NEW TRINIDEX SOLUTION, TRAVERT 10% (INVERT SUGAR) WITH VITAMINS IN WATER, provides more than 10 times the recommended daily allowances of thiamine, pyridoxine, and niacinamide, and more than 5 times the allowance of riboflavin as recommended by the National Research Council.

DISTRIBUTED AND AVAILABLE ONLY IN THE 37 STATES EAST OF THE ROCKIES (except in the city of El Paso, Texas) THROUGH
AMERICAN HOSPITAL SUPPLY CORPORATION
SCIENTIFIC PRODUCTS DIVISION GENERAL OFFICES • EVANSTON, ILLINOIS

Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the act of March 3, 1879. Published weekly at 8 Fenway, Boston 15. Domestic, $8.00 per year.

NOW! 2 *new* taste-tempting dosage forms of Pfizer-discovered tetracycline **TET**

TET

New standards for tetracycline therapy
in new ready-mixed liquid form . . .

NEW palatability
NEW convenience
NEW versatility

. . . the same unexcelled efficacy and toleration

RABON*

Brand of tetracycline

The outstanding modern broad-spectrum antibiotic, tetracycline, in a palate-pleasing raspberry-flavored homogenized mixture, standardized and ready-mixed at Pfizer Laboratories.

SUPPLIED: Bottles of 2 ounces and 1 pint. Each 5 cc. teaspoonful contains 125 mg. of tetracycline.

RABON SF†

Brand of tetracycline hydrochloride with vitamins

A fruit-mint flavored sugar-free homogenized mixture of tetracycline ready-mixed at Pfizer Laboratories and fortified with adequate quantities of B complex and vitamins C and K for nutritional support during stress.

TETRABON SF provides therapy on two levels:

1. anti-infective, against the pathogen
2. metabolic, assisting the patient physiologically.

SUPPLIED: Bottles of 2 ounces. Each 5 cc. teaspoonful contains 125 mg. of tetracycline plus the following formula:

Vitamin C as palmitate	*37.5 mg.*
Thiamine hydrochloride	*1.25 mg.*
Riboflavin	*1.25 mg.*
Niacinamide	*12.5 mg.*
Pyridoxine hydrochloride	*0.25 mg.*
Calcium pantothenate	*2.5 mg.*
Folic acid	*0.188 mg.*
Menadione (vitamin K analog)	*0.25 mg.*
Vitamin B_{12}	*0.5 mcg.*

Pfizer

*Trademark
†Trademark for Pfizer-originated, vitamin-fortified antibiotics

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.

1950 Cortone® | 1952 Hydrocortone®
1954 'Alflorone' | 1955 'Hydeltra'

DELTRA® tablets

(Prednisone, Merck) 5 mg. - 2.5 mg. - 1 mg. (scored)

the delta-1 analogue of cortisone

Indications:
Rheumatoid arthritis
Bronchial asthma
Inflammatory skin conditions

SHARP & DOHME
Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

Announcing

SEMINARS ON HYPNOSIS

Intensive Course on all Clinical Applications of Hypnosis

INDUCTION TECHNIQUES
HYPNOTHERAPY
HYPNODONTIA

ATTENDANCE LIMITED TO PHYSICIANS, DENTISTS, AND PSYCHOLOGISTS

CINCINNATI, OHIO
Nov. 18, 19, 20, 1955
Sponsored by
Ohio Valley Society of
Dental Psychosomatics

PHILADELPHIA, PA.
Dec. 9, 10, 11, 1955

INSTRUCTORS
Milton H. Erickson, MD
Wm. S. Kroger, MD
Leslie M. LeCron, AB
Seymour Hershman, MD
Irving Secter, DDS
Edward E. Aston, DDS

BUFFALO, NEW YORK
Jan. 20, 21, 22, 1956

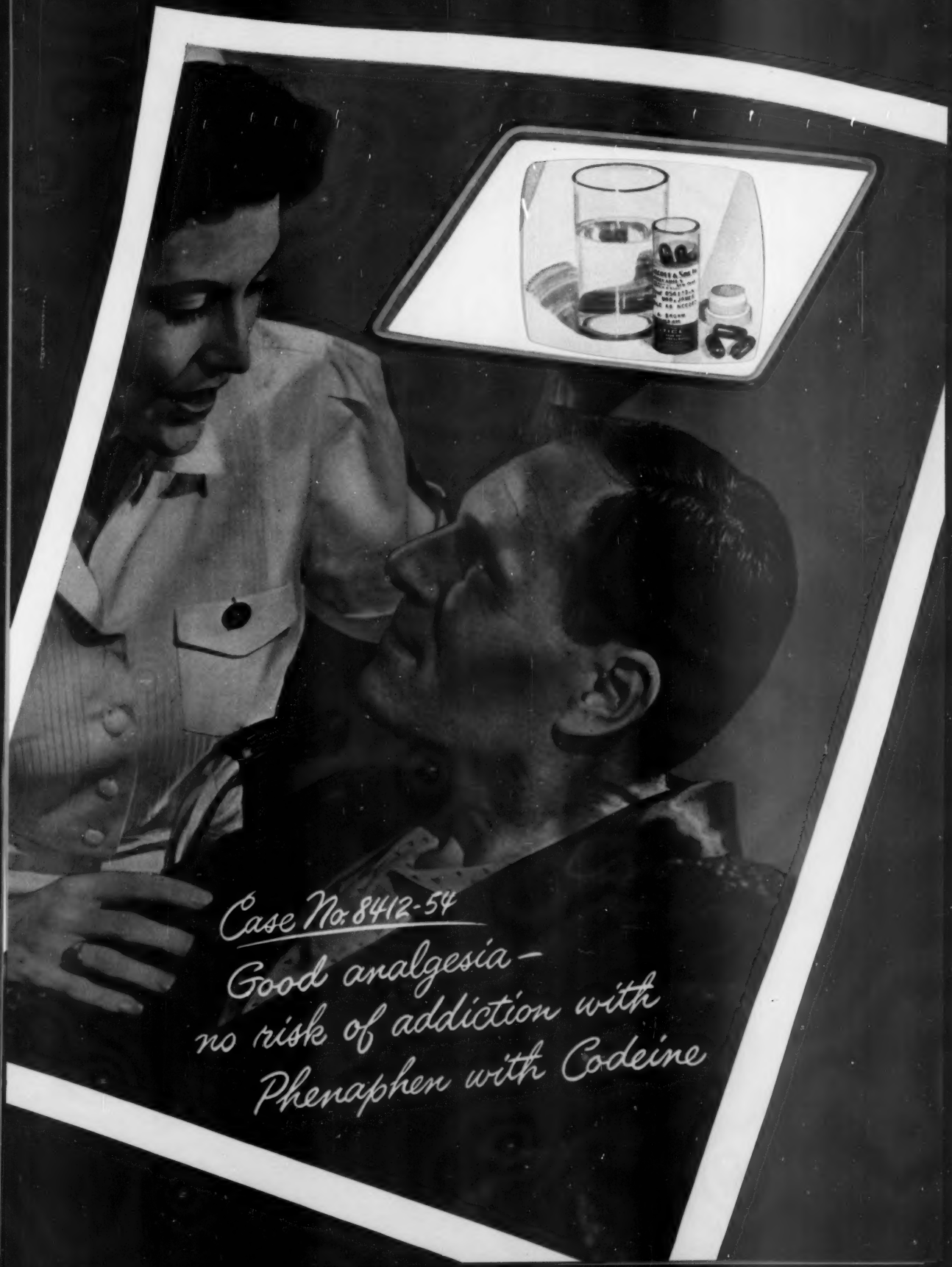
DETROIT, MICHIGAN
Feb. 24, 25, 26, 1956
Sponsored by
Michigan Society of
Dental Psychosomatics

For Further Information Write

MISS PAT MC FATE
Registrar

333 North Michigan Avenue Chicago, Illinois

AS FROM A PHYSICIAN'S ALBUM OF PRESCRIPTION SUCCESSES



Maximum safe

even in severe pain...

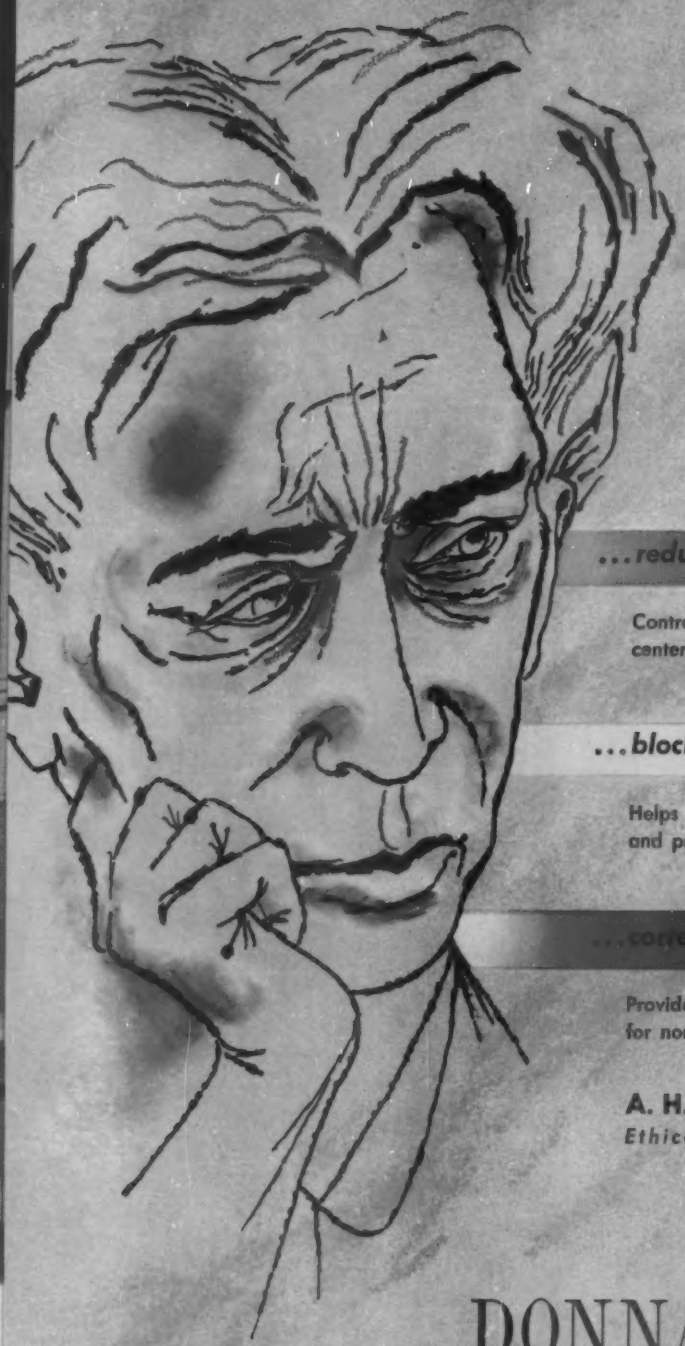
By the synergism of codeine phosphate with the ingredients of the Phenaphen formula, analgesic action is so enhanced that even the pain of late cancer is satisfactorily controlled in many cases. This maximum *safe* analgesia avoids the addiction hazard of morphine or of synthetic narcotics.

PHENAPHEN® with CODEINE

Robins

A. H. Robins Co., Inc., Richmond 20, Va.
Ethical Pharmaceuticals of Merit since 1878

analgesia–
the prescription behind the clinical success
Rx
Four
analgesic potencies to
meet individual requirements
PHENAPHEN®
(basic non-narcotic formula)
Acetylsalicylic acid 162 mg. (2½ gr.)
Phenacetin ..... 194 mg. (3 gr.)
Phenobarbital ..... 16.2 mg. (¼ gr.)
Hyoscyamine sulfate
0.031 mg. (1/2000 gr.)
(Brown and white capsules)
PHENAPHEN® with
CODEINE PHOSPHATE
¼ GR. (16.2 mg.)
(PHENAPHEN NO. 2)
(Black and yellow capsules)
PHENAPHEN® with
CODEINE PHOSPHATE
½ GR. (32.4 mg.)
(PHENAPHEN NO. 3)
(Black and green capsules)
PHENAPHEN® with
CODEINE PHOSPHATE
1 GR. (64.8 mg.)
(PHENAPHEN NO. 4)
(Green and white capsules)
new



FOR THE CHRONIC FATIGUE SYNDROME

Donnatal Plus

provides triple action

...reduces emotional hyperactivity

Controls cerebrogenic overactivation of autonomic centers by mild sedation.

...blocks parasympathetic over-stimulation

Helps prevent hyperinsulinism and hypoglycemia, and protects alimentary tract from hypermotility.

...corrects common nutritional deficiencies

Provides important B-complex vitamins essential for normal carbohydrate metabolism.

A. H. ROBINS CO., INC. · Richmond 20, Va.
Ethical Pharmaceuticals of Merit since 1878

DONNATAL® PLUS

Robins

(Donnatal with B Complex)

Each Tablet or 5 cc. teaspoonful of Elixir provides:

Hyoscyamine sulfate	0.1037 mg.	Riboflavin	2.0 mg.
Atropine sulfate	0.0194 mg.	Nicotinamide	10.0 mg.
Hyoscine hydrobromide	0.0065 mg.	Pantothenic acid	2.0 mg.
Phenobarbital (¼ gr.)	16.2 mg.	Pyridoxine hydrochloride	0.5 mg.
Thiamine	3.0 mg.		

BLUE
AT
BREAKFAST?

BONADOXIN*

(BRAND OF MECLIZINE HCL, PYRIDOXINE HCL)

stops morning sickness

RESULTS
of
this
new
COMBINATION

In 100 patients with severe nausea and vomiting, Weinberg reports 88% good to excellent results.[1] In another series, BONADOXIN abolished vomiting in 40 of 41 gravida, eliminated nausea in 30 of the 41.[2]

Each BONADOXIN tablet contains:

MECLIZINE HCl	25 mg.
PYRIDOXINE HCl	50 mg.

Mild cases: One BONADOXIN tablet at bedtime.
Severe cases: One at bedtime and on arising.
In bottles of 25 and 100, prescription only.
Also indicated in post-radiation sickness, nausea following surgery, Ménière's syndrome.

1. Weinberg, Arthur and Werner, W. E. F.: Bonadoxin, a new effective oral therapy for hyperemesis gravidarum. Am. Pract. and Dig. of Treatment. In press. 2. Personal communication. 3. Berenson, F.: Bonadoxin: oral therapy for nausea and vomiting of pregnancy. In press.

ROERIG Rx
Chicago 11, Illinois
*TRADEMARK

Pork in the Dietary
During Pregnancy and Lactation

CERTAIN NUTRIENTS are required in greater than normal amounts during pregnancy and lactation. Pork meat, though its cost is low, supplies a remarkably high quantity of the nutrients required by the maternal organism in these periods of physiologic need.

During pregnancy the maternal organism may store 3.3 to 5.5 pounds of protein in excess of that contributed to fetal tissue.[1] Enough iron is stored to approximate the entire amount secreted in the milk during 9 months of lactation, in addition to the iron supplied to the fetus.[2]

The body of the newborn infant contains approximately 500 grams of protein, 14 grams of phosphorus, and 0.5 gram of iron.[3] It is estimated that the lactating mother, through breast milk, provides a 26 week old infant with about 12 grams of protein, 76 grams of lactose, and 1.2 mg. of iron each day.[2]

Pork meat, an excellent source of high quality protein, thiamine, niacin, and iron,[4] also supplies valuable amounts of other B vitamins, as well as phosphorus, magnesium, and potassium. The thiamine content of pork is particularly important, since there are few more valuable food sources of this vitamin.[4]

Pork and pork sausage—economical, good tasting—are valuable components of the dietary of the pregnant or lactating woman. Just how valuable, is shown in the table below.

1. Toverud, K.U.; Stearns, G., and Macy, I.G.: Maternal Nutrition and Child Health, an Interpretative Review, Washington, D.C., National Research Council, Bull. 123, 1950.

2. McLester, J.S., and Darby, W.J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W.B. Saunders Company, 1952, p. 241.

3. Marrack, J.R.: Food and Planning, London, Victor Gollancz, Ltd., 1943, p. 67.

4. Wolgamot, I.H., and Fincher, L.J.: Pork Facts for Consumer Education, Washington, D.C., United States Department of Agriculture, AIB No. 109, 1954.

5. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared, Washington, D.C., United States Department of Agriculture, Agricultural Handbook No. 8, 1950.

6. Bowes, A. deP., and Church, C.F.: Food Values of Portions Commonly Used, ed. 7, Philadelphia, Anna dePlanter Bowes, 1951.

Percentages of Recommended Daily Dietary Allowances* for Pregnant (3rd Trimester) and Lactating Women Provided by 3-Ounce Portions of Cooked Pork Meats and Pork Sausage

	Protein	Iron	Phosphorus	Thiamine	Riboflavin	Niacin	Calories
PREGNANCY (3rd trimester)							
Ham, without bone, 3 oz., cooked[5]	25.0%	17.3%	13.5%	30.0%	10.0%	26.7%	12.5%
Pork Chops, without bone, 3 oz., cooked[5]	25.0%	17.3%	13.3%	47.3%	10.0%	28.7%	10.5%
Pork Sausage, 3 oz., cooked[6]	17.3%	14.0%	9.2%	27.7%	10.1%	18.5%	14.7%
LACTATION							
Ham, without bone, 3 oz., cooked[5]	20.0%	17.3%	10.1%	30.0%	8.0%	26.7%	10.2%
Pork Chops, without bone, 3 oz., cooked[5]	20.0%	17.3%	10.0%	47.3%	8.0%	28.7%	8.6%
Pork Sausage, 3 oz., cooked[6]	13.8%	14.0%	6.9%	27.7%	8.1%	18.5%	12.0%

*Recommended Dietary Allowances, Washington, D. C., National Academy of Sciences—National Research Council, Publication 302, 1953

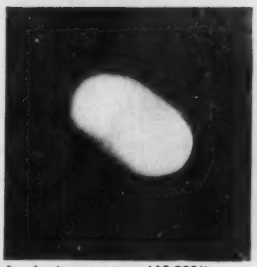
The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute
Main Office, Chicago... Members Throughout the United States

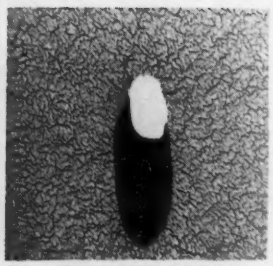
The organisms commonly involved in

Pyelitis

E. coli (8,000X)

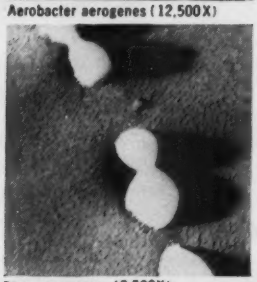


Aerobacter aerogenes (12,500X)

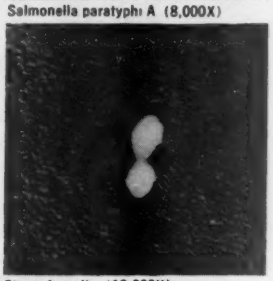


Salmonella paratyphi A (8,000X)

Salmonella paratyphi B (6,500X)



Strep. pyogenes (8,500X)



Strep. faecalis (10,000X)

Strep. viridans (9,000X)

Staph. aureus (9,000X)

Upjohn

ELECTRON MICROGRAPHS

***All* of them are included in the more than 30 organisms susceptible to broad-spectrum**

PANMYCIN*

HYDROCHLORIDE

100 mg. and 250 mg. capsules • 125 mg. and 250 mg./tsp. oral suspension (PANMYCIN Readimixed)
100 mg./cc. drops • 100 mg./2 cc. injection, intramuscular
100 mg., 250 mg., and 500 mg. vials, intravenous

*TRADEMARK, REG. U. S. PAT. OFF.—THE UPJOHN BRAND OF TETRACYCLINE

Latest data on effectiveness of Furadantin®

brand of nitrofurantoin, Eaton

in urinary tract infections

Investigators:

Flippin, H. F., and Eisenberg, G. M.: Antimicrobial Therapy in Medical Practice, Philadelphia, F. A. Davis Co., 1955, p. 40.

Latest data on effectiveness of Furadantin

Clinical studies have demonstrated rapid clinical response in cases of cystitis and pyelonephritis, including infections caused by refractory organisms.

Trafton, H. M., et al.: New England J. Med. **252:** 383, 1955.

13 acute cases . . . 6 appeared cured . . . 6 markedly improved with no relapses.

36 chronic infections: 30 showed symptomatic improvement, frequently within 24 hours.

Beutner, E. H., et al.: Antibiotics Annual, 1954-1955, New York, Medical Encyclopedia, Inc., 1955, p. 988.

30 chronic urinary tract infections: Of 47 strains of bacteria isolated from these patients, 29 strains (62%) were eradicated by Furadantin.

Hasen, H. B., and Moore, T. D.: J.A.M.A. **155:** 1470, 1954.

Of patients with acute urinary tract infections, 95.7% were benefited. Patients with chronic infections and those with organic or obstructive lesions were benefited in 82% of cases.

Dosage — average adult: four 100 mg. tablets daily, 1 tablet with each meal and 1 tablet on retiring, with food or milk.

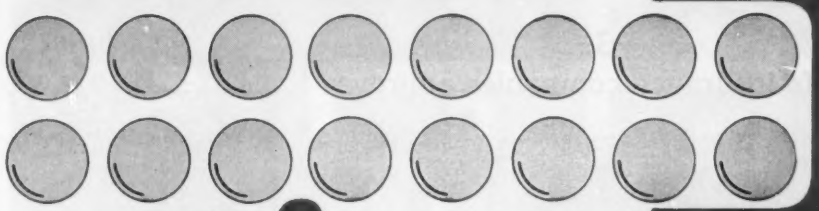
Furadantin tablets, 50 and 100 mg. in bottles of 25 and 100. Furadantin Oral Suspension (5 mg. per cc.), bottle of 4 fl.oz. (118 cc.).

EATON LABORATORIES
NORWICH • NEW YORK

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS O_2N PRODUCTS OF EATON RESEARCH

WHICH WOULD *YOUR* PATIENTS PREFER?

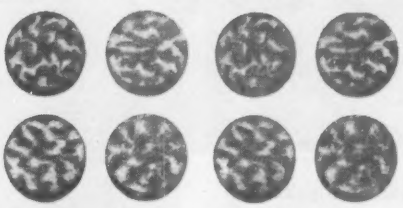
16 **ONE-HALF GRAM** ENTERIC-COATED
AMMONIUM CHLORIDE TABLETS



or only **8**

AMCHLOR

ONE GRAM ENTERIC-COATED
AMMONIUM CHLORIDE TABLETS *(Brewer)*



"Easy-to-swallow" AMCHLOR is processed in such a manner that each enteric-coated tablet contains 1 Gram of ammonium chloride and yet is not much larger than the 7½ gr. enteric-coated tablet. Thus the same dose can be given with only one-half the number of tablets.

FROM COAST TO COAST both physicians and patients are showing a decided preference for **AMCHLOR.**

SUPPLIED
bottles of 100, 500 and 1000

The next time you prescribe ammonium chloride
specify—
AMCHLOR – Brewer
THE ONE GRAM enteric-coated tablet
of ammonium chloride
for your patients' convenience!

For samples just send your Rx blank marked — 26AM11

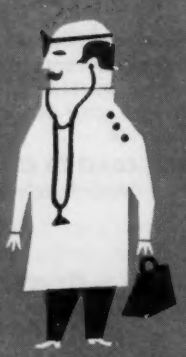
Brewer
EST. 1852

BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.

395
life insurance companies approve

CLINITEST®
BRAND
for rapid, reliable urine-sugar testing

reliability and standardization recognized by
9 out of 10 leading insurance companies *
convenience and time-saving appreciated by
thousands of examining physicians
* Recent survey of 437 insurance companies

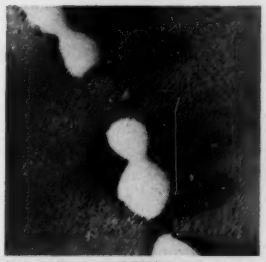


AMES DIAGNOSTICS
Adjuncts in Clinical Management

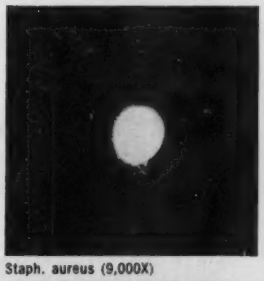
AMES COMPANY, INC • ELKHART, INDIANA
Ames Company of Canada, Ltd., Toronto

The organisms commonly involved in

Acute Pharyngitis



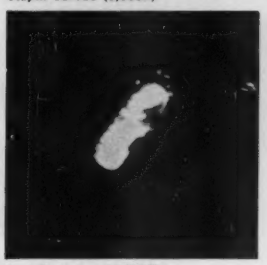
Strep. pyogenes (8,500X)



Staph. aureus (9,000X)

D. pneumoniae (10,000X)

N. intracellularis (5,000X)



H. influenzae (16,000X)

C. diphtheriae (6,000X)

K. pneumoniae (13,000X)

Upjohn

ELECTRON MICROGRAPHS

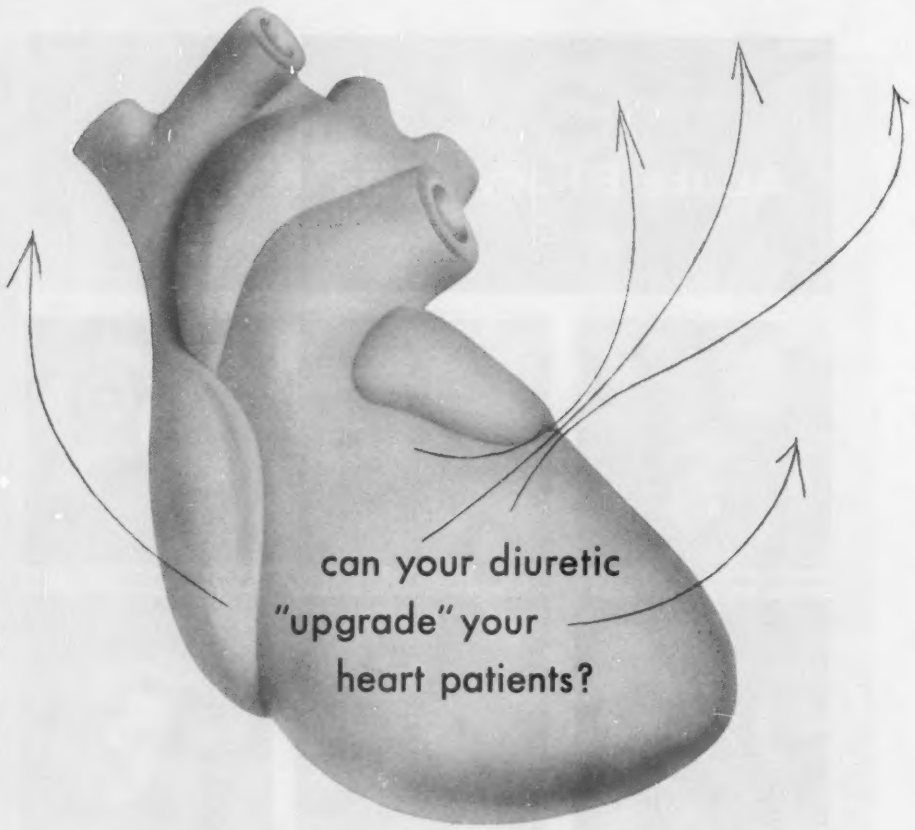
***All* of them are included in the more than 30 organisms susceptible to broad-spectrum**

PANMYCIN*

HYDROCHLORIDE

100 mg. and 250 mg. capsules • 125 mg. and 250 mg./tsp. oral suspension (PANMYCIN Readimixed) 100 mg./cc. drops • 100 mg./2 cc. injectable, intramuscular 100, 250, and 500 mg./injection, intravenous

*TRADEMARK, REG. U. S. PAT. OFF.—THE UPJOHN BRAND OF TETRACYCLINE



know your diuretic

fewer restrictions of activity are the benefit of prolonged use of those diuretics effective over the entire range of cardiac failure. The organomercurials—parenteral and oral—improve the classification and prognosis of your decompensated patients. Diuretics of value only in milder grades of failure, or which must be given intermittently because of refractoriness or side effects, are incapable of "upgrading" the cardiac patient.

TABLET
NEOHYDRIN®
BRAND OF CHLORMERODRIN
(18.3 MG. OF 3-CHLOROMERCURI-2-METHOXY-PROPYLUREA IN EACH TABLET)

for "...a new picture of the patient in congestive heart failure."*
replaces injections in 80% to 90% of patients
*Leff, W., and Nussbaum, H. E.: J. M. Soc. New Jersey 50:149, 1953.

a standard for initial control of severe failure

MERCUHYDRIN® SODIUM
BRAND OF MERALLURIDE INJECTION

Leadership in diuretic research
Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

in rheumatoid arthritis

- greater therapeutic benefits
- fewer unwanted effects

METICORTELONE

PREDNISOLONE, SCHERING

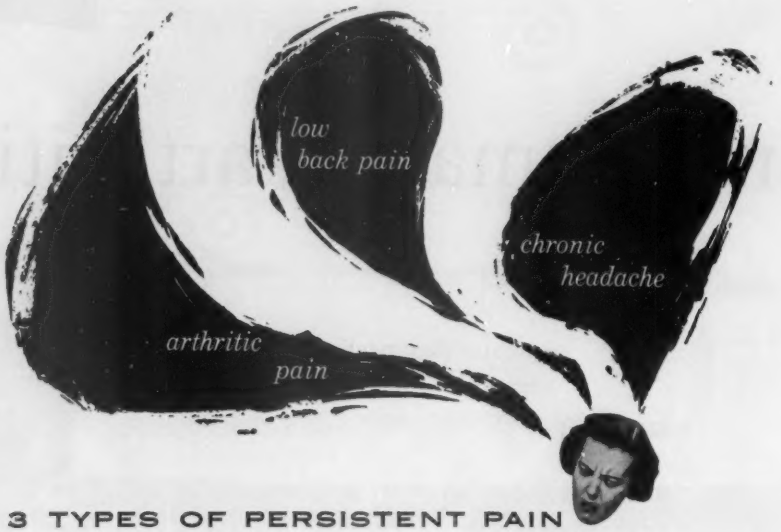
METICORTELONE resembles METICORTEN in antirheumatic, anti-inflammatory and antiallergic effectiveness.[1-11] The availability of these new steroids, first discovered and introduced by Schering, provides the physician with two valuable agents for safer, more effective cortical hormone therapy.

Bibliography: (1) Bunim, J. J.; Pechet, M. M., and Bollet, A. J.: J.A.M.A. *157*:311, 1955. (2) Waine, H.: Bull. Rheumat. Dis. *5*:81, 1955. (3) Tolksdorf, S., and Perlman, R.: Fed. Proc. *14*:377, 1955. (4) Herzog, H. L., and others: Science *121*:176, 1955. (5) Bunim, J. J.; Black, R. L.; Bollet, A. J., and Pechet, M. M.: Ann. New York Acad. Sc. *61*:358, 1955. (6) Henderson, E.: New developments in steroid therapy of rheumatic diseases, presented at New Jersey State Medical Society Meeting, Atlantic City, New Jersey, April 17-20, 1955. (7) Boland, E. W.: California Med. *82*:65, 1955; abs., Curr. M. Digest *22*:53, 1955. (8) King, J. H., and Weimer, J. R.: A.M.A. Arch. Ophth. *54*:46, 1955. (9) Criep, L. H.: Prednisolone and prednisone in the treatment of allergic diseases, to be published. (10) Sternberg, T. H., and Newcomer, V. D.: Am. Pract. & Digest Treat. *6*:1102, 1955. (11) Gordon, D. M.: Prednisone and prednisolone in ocular disease, to be published.

Schering

METICORTELONE,* brand of prednisolone, Schering.
METICORTEN,* brand of prednisone, Schering.
*T. M.

ML-J-55



3 TYPES OF PERSISTENT PAIN

with psychic side effects

As the conditions that cause these types of pain persist, the patient becomes more and more preoccupied with his pain. The depression, nervous tension and anxiety that nearly always accompany such pain combine to intensify and prolong it.

'Daprisal' relieves these psychic aspects of pain because it provides the mood-ameliorating effect of Dexamyl* (Dexedrine† and amobarbital). It brings about a feeling of energy and well-being, and restores optimism.

'Daprisal' works to relieve the pain itself because it provides the combined analgesic effect of acetylsalicylic acid and phenacetin, *potentiated* by amobarbital.

DAPRISAL*

for the relief of pain and psychic side effects of pain

Smith, Kline & French Laboratories, Philadelphia 1

FORMULA: Each 'Daprisal' tablet contains 'Dexedrine' Sulfate (dextro-amphetamine sulfate, S.K.F.), 5 mg.; amobarbital, ½ gr. (32 mg.); acetylsalicylic acid, 2½ gr. (0.16 Gm.); phenacetin, 2½ gr. (0.16 Gm.).

*T.M. Reg. U.S. Pat. Off.
†T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

ORAL PENICILLIN: A CHALLENGE ANSWERED

Through the years, the paradox of penicillin has been this—that while injectable forms have become the sheet anchor of antibiotic therapy, oral forms have all too often posed perplexing problems.

How to ensure survival in gastric acid? How to get maximal absorption? How to increase the antibacterial effect? How, indeed, to realize the hope at the dawn of the penicillin era that the oral route might even merit selective preference?

These have been the challenges. Out of them has come PEN·VEE·*Oral*—a remarkable innovation among oral penicillins. For PEN·VEE·*Oral* is penicillin V, the unique penicillin stable as a free acid—a penicillin with such special characteristics that it opens new horizons in oral penicillin therapy.

Because PEN·VEE·*Oral* is acid-stable, it is almost entirely unaffected by gastric juices. Because it is completely soluble in alkaline media, it is readily and optimally absorbed as active penicillin in the duodenum. Clinical results include prompt, high blood levels, maximal effect from the administered dose, a wide margin of toleration.

For these striking advantages, acquaint yourself with PEN·VEE·*Oral* in your practice.

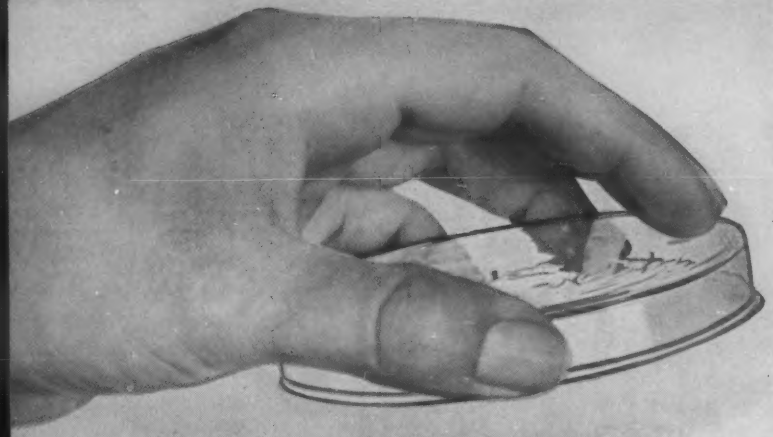
Supplied: Tablets, 125 mg. (200,000 units) each, bottles of 36. Also available: BICILLIN®-Vee Tablets, 100 mg. (100,000 units) benzathine penicillin G and 62.5 mg. (100,000 units) penicillin V, bottles of 36.

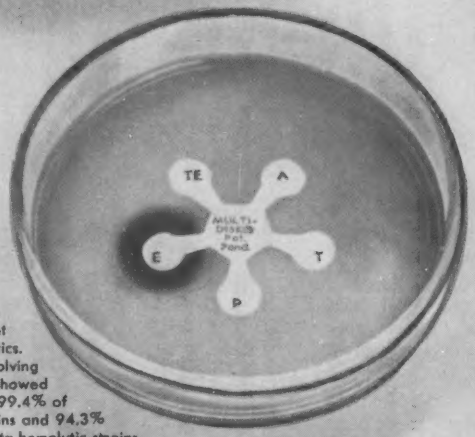
PEN·VEE·*Oral**

Penicillin V, Crystalline
Phenoxymethyl Penicillin

*Trademark

Wyeth
PHILADELPHIA, PA.





DESTROYS ENTEROCOCCI

This blood agar plate shows a strain of *beta* hemolytic enterococcus. Note extreme sensitivity of this organism to ERYTHROCIN—yet it easily resists the other antibiotics. Additional data: A study[1] involving 202 enterococcic strains showed sensitivity to erythromycin in 99.4% of *alpha* hemolytic strains and 94.3% of *beta* hemolytic strains.

specific against coccic infections

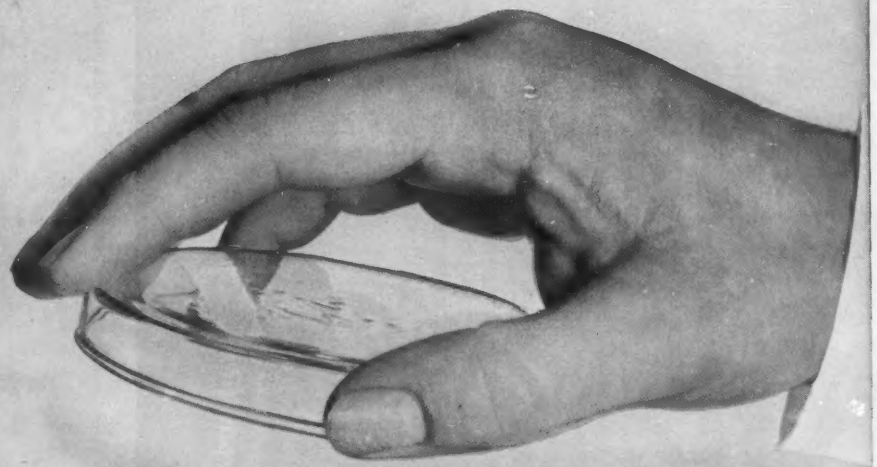
Now, you can prescribe *specific therapy* against staph-, strep- or pneumococci by simply writing *Filmtab* ERYTHROCIN Stearate. Since this coccic group causes most bacterial respiratory infections (and since these organisms are the very ones most sensitive to ERYTHROCIN) doesn't it make good sense to prescribe *Filmtab* ERYTHROCIN when the infection is coccic?

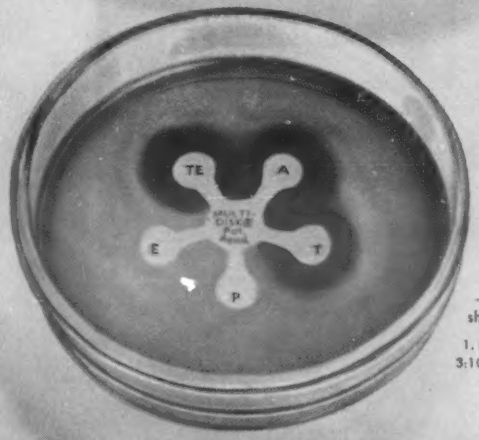
filmtab®

Erythrocin®

Erythromycin Stearate, Abbott)

STEARATE





SPARES
INTESTINAL FLORA

This sensitivity test shows ERYTHROCIN and the same antibiotics against a typical intestinal strain of *E. coli*. Note that ERYTHROCIN and penicillin do not affect this gram-negative organism —although the other antibiotics show marked inhibitory action.

1. Eisenberg, et al., Antib. & Chemo., 3:1026-1028, Oct., 1953.

with little risk of serious side effects

Since ERYTHROCIN is inactive against gram-negative organisms, it is less likely to alter intestinal flora—with an accompanying low incidence of side effects. Also, your patients seldom get the allergic reactions sometimes seen with penicillin. Or loss of accessory vitamins during ERYTHROCIN therapy. *Filmtab* ERYTHROCIN Stearate (100 and 200 mg.) is supplied in bottles of 25 and 100 at pharmacies everywhere. Abbott

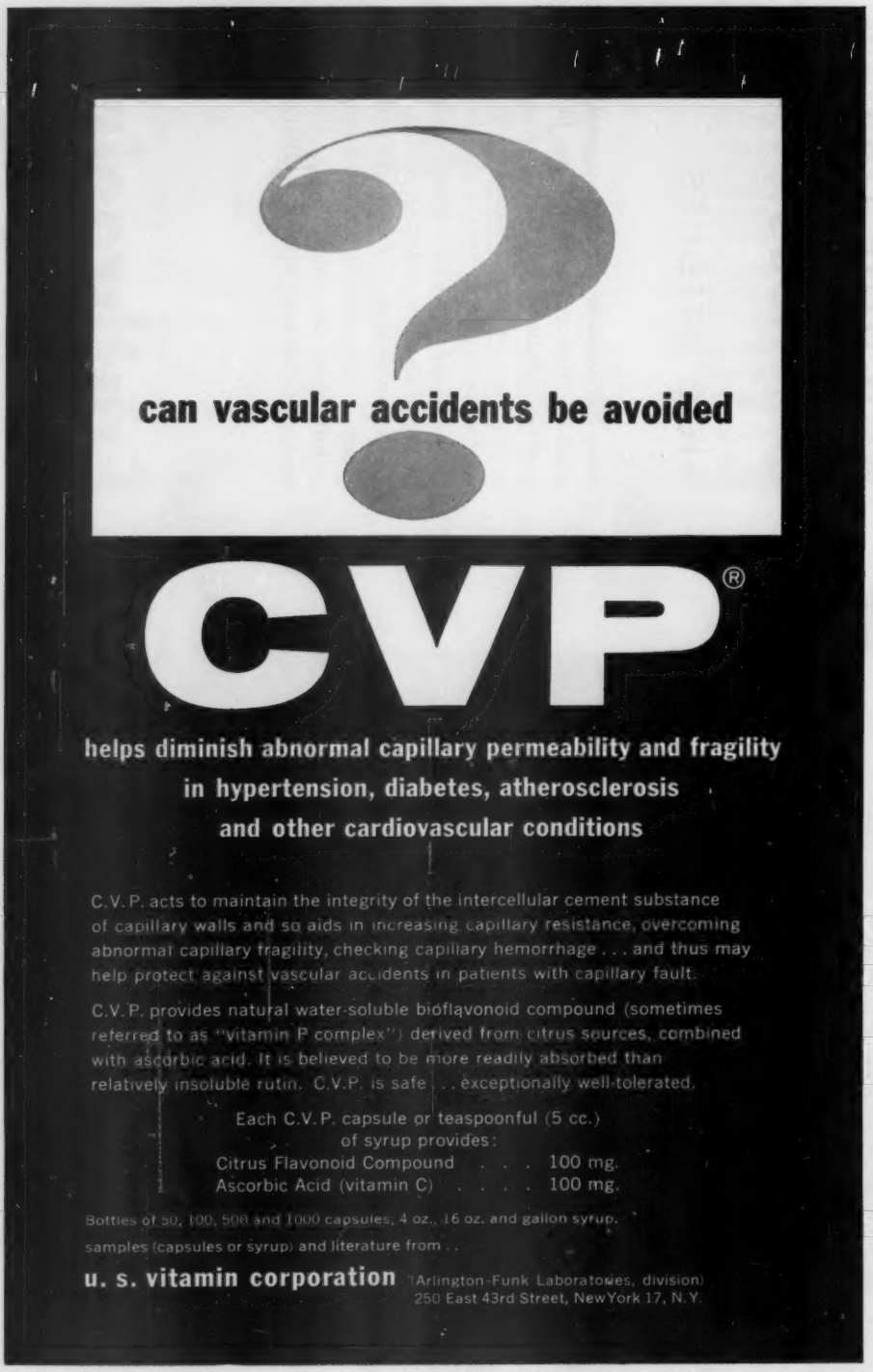
filmtab®

Erythrocin®

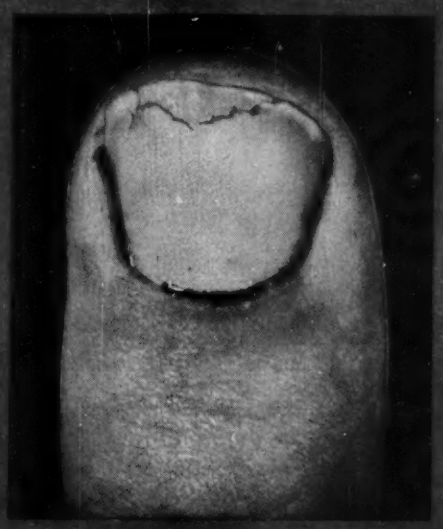
(Erythromycin Stearate, Abbott)
STEARATE

® Filmtab—Film sealed tablets; patent applied for.

508183


can vascular accidents be avoided
CVP®
helps diminish abnormal capillary permeability and fragility
in hypertension, diabetes, atherosclerosis
and other cardiovascular conditions
C.V.P. acts to maintain the integrity of the intercellular cement substance of capillary walls and so aids in increasing capillary resistance, overcoming abnormal capillary fragility, checking capillary hemorrhage . . . and thus may help protect against vascular accidents in patients with capillary fault.
C.V.P. provides natural water-soluble bioflavonoid compound (sometimes referred to as "vitamin P complex") derived from citrus sources, combined with ascorbic acid. It is believed to be more readily absorbed than relatively insoluble rutin. C.V.P. is safe . . . exceptionally well-tolerated.
Each C.V.P. capsule or teaspoonful (5 cc.) of syrup provides:
Citrus Flavonoid Compound . . . 100 mg.
Ascorbic Acid (vitamin C) . . . . 100 mg.
Bottles of 50, 100, 500 and 1000 capsules, 4 oz., 16 oz. and gallon syrup.
samples (capsules or syrup) and literature from . .
u. s. vitamin corporation (Arlington-Funk Laboratories, division)
250 East 43rd Street, New York 17, N.Y.

KNOX Protein Previews



New Study Shows Gelatine
Restores Brittle Fingernails to Normal

Directions for making the Knox Gelatine drink in every package

Brittle, fragile or laminating fingernails are the bane of many a woman's existence. Yet this highly prevalent and distressing condition often has gone uncontrolled for lack of effective therapy. Now, you can promise these patients substantial relief in a large percentage of cases.

In a recent study[1] that confirmed previous work[2] Knox Gelatine was used to treat 36 women with fragile, brittle, laminating fingernails. The response was most gratifying. Except for three patients who discontinued the therapy, three diabetics, and two women who had congenital deformities, the splitting ceased and all other patients were able to manicure their nails to a full point by the time the study ended.

Optimal dosage proved to be one envelope (7 grams) of Knox Gelatine administered daily for three months. Improvement, however, was noted after the first month. If you would like more complete details of this work, just use the coupon.

1. Rosenberg, S. and Oster, K. A., "Gelatine in the Treatment of Brittle Nails," *Conn. State Med. J.* **19**:171-179, March 1955.
2. Tyson, T. L., *J. Invest. Dermat.* **14**:323, May 1950.

Chas. B. Knox Gelatine Company, Inc.
Professional Service Dept. NE-11
Johnstown, N. Y.

Please send me a reprint of the article by Rosenberg and Oster with illustrated color brochure.

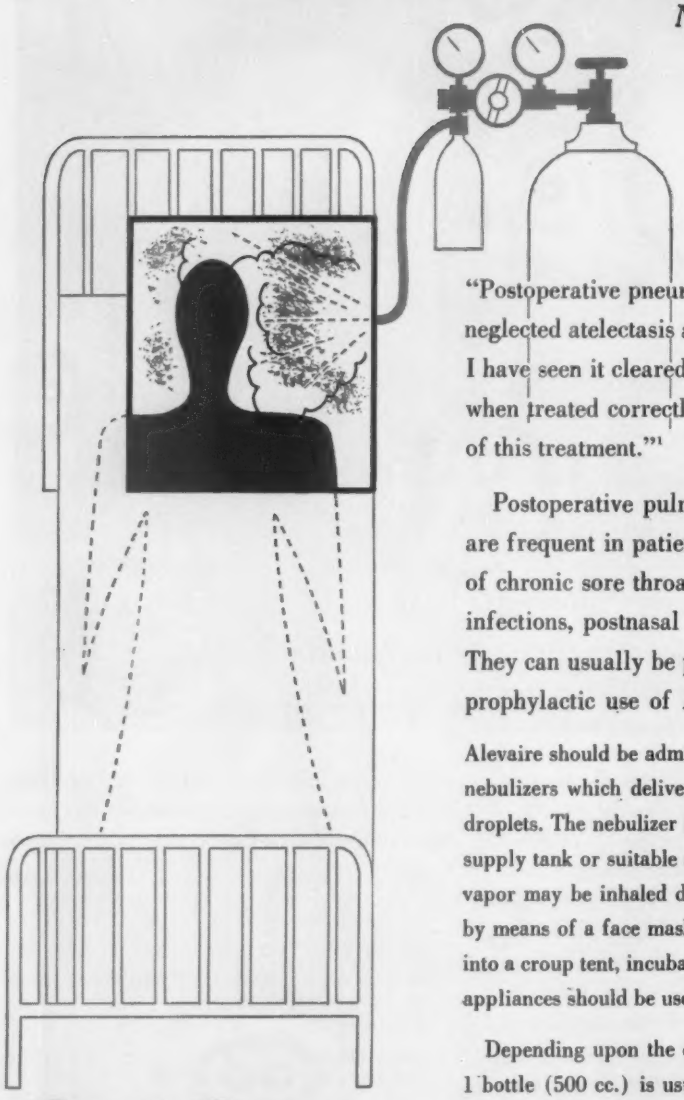
YOUR NAME AND ADDRESS

prevent

POSTOPERATIVE PULMONARY COMPLICATIONS

with **ALEVAIRE®**

Nontoxic Mucolytic Mist



"Postoperative pneumonia is almost always neglected atelectasis and must be treated as such. I have seen it cleared up within a few hours when treated correctly. Alevaire is part of this treatment."[1]

Postoperative pulmonary complications are frequent in patients with a history of chronic sore throat, chronic cough, sinus infections, postnasal drip or heavy smoking. They can usually be prevented by the prophylactic use of Alevaire.

Alevaire should be administered only by aerosol nebulizers which deliver a fine mist without large droplets. The nebulizer is attached to an oxygen supply tank or suitable air compressor. The Alevaire vapor may be inhaled directly from the nebulizer by means of a face mask, or it may be delivered into a croup tent, incubator or special tent; only those appliances should be used which deliver a fine mist.

Depending upon the output of the nebulizing device 1 bottle (500 cc.) is usually sufficient to last from eight to twenty-four hours.

Supplied in bottles of 60 cc. and 500 cc.

Winthrop-Stearns INC.
NEW YORK 18, N. Y. • WINDSOR, ONT.

1. Sadove, M.S.: Paper read at Meeting of the Champaign County Medical Society, Champaign, Ill., Mar. 12, 1953.

Alevaire, trademark reg. U. S. Pat. Off.

The New England
Journal of Medicine

Copyright, 1955, by the Massachusetts Medical Society

Volume 253 NOVEMBER 3, 1955 Number 18

ADVANCES IN THE DIAGNOSIS OF ALTERED STATES OF ADRENOCORTICAL FUNCTION*

JOHN C. LAIDLAW, M.D.,† WILLIAM J. REDDY, A.B.,‡ DALTON JENKINS, M.D.,§
NAJIB ABU HAYDAR, M.D.,¶ ALBERT E. RENOLD, M.D.,‖ AND GEORGE W. THORN, M.D.**

BOSTON

GREAT advances in the diagnosis of altered states of adrenocortical function have been made possible by improvements in methods of steroid analysis and by the availability of purified preparations of ACTH and adrenocortical hormones. The development of simple methods for the measurement of blood and urinary 17-hydroxycorticoids has facilitated the estimation of the quantity of hydrocortisone secreted by the human adrenal cortex.[1,2] The availability of ACTH has opened the way to the exploration of adrenocortical reserve in a wide variety of physiologic and pathologic states. It now appears that the intravenous administration of ACTH with the determination of 17-hydroxycorticoids and 17-ketosteroids in blood or urine provides the most accurate means of quantitating adrenocortical response.[3,4] Finally, the large-scale preparation of cortisone, hydrocortisone and more particularly, a highly potent derivative, 9-alpha-fluorohydrocortisone,[5] has provided substances capable of inhibiting ACTH secretion. The study of urinary 17-hydroxycorticoids after fluorohydrocortisone administration and of the urinary 17-ketosteroids after the administration of all three compounds has made it possible to determine the degree of dependency of the adrenal cortex on the anterior pituitary gland in states of adrenal dysfunction in man.

*From the Department of Medicine, Harvard Medical School, and the Medical Service, Peter Bent Brigham Hospital.

Supported by funds from the National Institutes of Health of the United States Public Health Service, the Eugene Higgins Trust of Harvard Medical School, the John A. Hartford Foundation, New York City, and the Medical Research and Development Board, Office of the Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-135.

†Associate in medicine, University of Toronto Faculty of Medicine; formerly, instructor in medicine, Harvard Medical School, junior associate in medicine, Peter Bent Brigham Hospital, and Markle Scholar in Medical Sciences.

‡Chemist, Peter Bent Brigham Hospital.

§Assistant professor of medicine, University of Colorado School of Medicine; formerly, instructor in medicine, Harvard Medical School, junior associate in medicine, Peter Bent Brigham Hospital, and Markle Scholar in Medical Sciences.

¶Research fellow in medicine, Harvard Medical School; assistant in medicine, Peter Bent Brigham Hospital; Damon Runyon Memorial Fund Research Fellow.

‖Instructor in medicine, Harvard Medical School; junior associate in medicine, Peter Bent Brigham Hospital.

**Hersey Professor of the Theory and Practice of Physic, Harvard Medical School; physician-in-chief, Peter Bent Brigham Hospital.

METHODS

In the present studies the total urinary 17-hydroxycorticoids were determined by the method of Reddy, Jenkins and Thorn,[2] in which the values in normal subjects range from 1 to 10 mg. per day, with a mean of 4.8 mg. in males and 3.8 mg. in females. Urinary 17-ketosteroids were measured by a modification of the method of Drekter et al.,[6] whereby the colorimetry was performed as in the procedure of Holtorff and Koch.[7] With this procedure the normal values range in males from 14 to 25 mg. per day, with a mean of 18 mg., and in females from 8 to 14 mg. per day, with a mean of 11 mg. Blood eosinophil counts were carried out as previously described.[8]

The two-day intravenous ACTH tests were performed as follows[4]: 25 *U.S.P.* units of the hormone were infused intravenously in 500 cc. of physiologic saline solution or 5 per cent dextrose in water over an eight-hour period on each of two successive days. The infusions were started between 8 and 10 a.m. The patients were not fasted during the procedure. Determinations of urinary 17-ketosteroids and 17-hydroxycorticoids were carried out on twenty-four-hour collections (7 a.m. - 7 a.m.) on two or more control days and on the two days of ACTH administration. Blood was drawn for an eosinophil count at the beginning and at the end of the ACTH infusion.

OBSERVATIONS

Response to ACTH in Patients with Intact Adrenal Glands

The results obtained with the two-day intravenous ACTH test in 40 *adult hospitalized* patients in whom there was no evidence of endocrine disease are shown in Figure 1. For the 17-ketosteroids the increment over the average control excretion ranged from 0 to 8.3 mg. (mean, 4 mg.) on the first day of ACTH administration and from 1.8 to 10.9 mg. (mean, 6 mg.) on the second day. For the 17-hydroxycorticoids the

increment ranged from 5 to 25 mg. (mean, 14 mg.) on the first ACTH day and from 15 to 41 mg. (mean, 24 mg.) on the second. On both days of ACTH administration an eosinopenia (80 to 100 per cent) was observed in these subjects. Although adrenocortical stimulation with intravenously administered ACTH permits the most definitive evaluation of adrenocortical reserve, alternate methods of administering

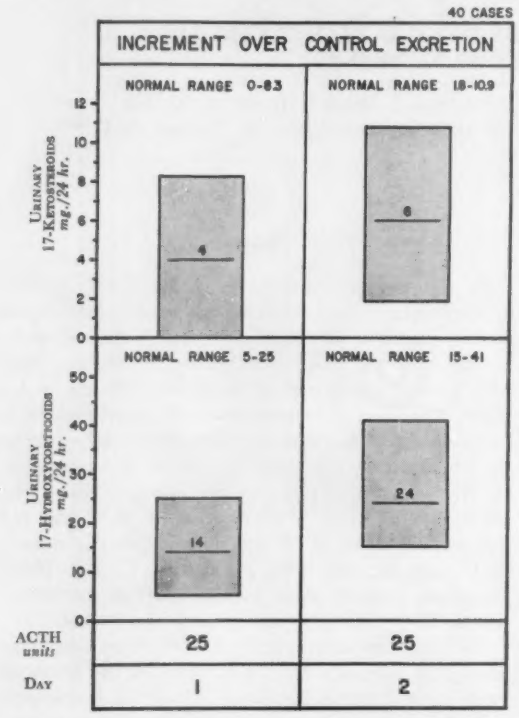


FIGURE 1. *Adrenal Response to the Two-Day Intravenous ACTH Test in 40 Patients without Evidence of Endocrine Disease.*

ACTH for screening purposes have recently been described and reviewed by Jenkins et al.[4]

Diagnosis of Adrenocortical Insufficiency

Primary failure (Addison's disease). Patients with Addison's disease failed to show an adrenocortical response to ACTH.[4] No appreciable rise in urinary 17-ketosteroids or 17-hydroxycorticoids occurred, and no significant fall in the level of circulating eosinophils was observed. In fact a rise in the eosinophil count was frequently seen.

Recent observations with 9-alpha-fluorohydrocortisone acetate, a highly potent derivative of hydrocortisone, have indicated that small quantities (0.25 to 1.0 mg. per day) of this hormone given by mouth serve as adequate maintenance therapy in patients with Addison's disease.[5] In contrast to the effect of maintenance doses of cortisone or hydrocortisone, these small doses of fluorohydrocortisone make no appreciable contribution to the urinary 17-ketosteroids and 17-hydroxycorticoids. Furthermore, fluorohydrocortisone administration protects the patient with Addison's disease against an untoward reaction to ACTH. Thus, with the administration of this steroid it is possible to carry out the intravenous ACTH test and to follow accurately the urinary steroid response in patients with suspected adrenal insufficiency without in any way compromising their clinical condition. The use of fluorohydrocortisone in association with the two-day ACTH test in a forty-three-year-old woman with primary adrenal insufficiency is shown in Figure 2.

In the male patient with Addison's disease the urinary 17-ketosteroid level is diminished, whereas in the female it approaches 0. The control level of urinary 17-hydroxycorticoids in the majority of male and female patients is below 1 mg. per day. In 7 patients with definite clinical evidence of Addison's disease, however, 17-hydroxycorticoid levels higher than 1 mg. per 24 hours have been observed (Fig. 3). In 5 of these patients the urine was examined by means of paper chromatography after glucuronidase hydrolysis; tetrahydrocortisone and tetrahydrohydro-

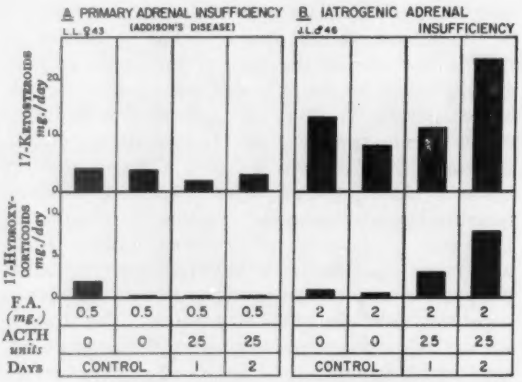


FIGURE 2. *Response to ACTH in Adrenocortical Insufficiency.*

A = patient maintained on cortisone, 25 mg. by mouth, daily for two years before the present study. The cortisone was discontinued and the fluorohydrocortisone acetate (F.A.) started by mouth two days before the ACTH test.

B = patient considered to have Addison's disease and maintained on 50 mg. of cortisone by mouth daily for two years before observation. The cortisone was discontinued and the fluorohydrocortisone started by mouth two days before the ACTH test. (This patient was subsequently found to have salt-losing nephritis.)

cortisone, the major known metabolites of hydrocortisone, were found.[9] Despite this evidence of endogenous hydrocortisone secretion, in none of these patients was there an adrenocortical response to ACTH. Three similar patients have been described by Perkoff et al.[10] It seems probable that in such cases a remnant of adrenocortical tissue is being stimulated maximally by endogenous ACTH and is therefore refractory to further ACTH stimulation. This

hypothesis is strengthened by the observation that fluorohydrocortisone administered to a patient with Addison's disease with similar findings resulted in the disappearance of measurable amounts of 17-hydroxycorticoids from the urine.

It is apparent from the studies described above that since some patients with Addison's disease may have detectable quantities of 17-hydroxycorticoids in their urine and since normal persons occasionally exhibit low 17-hydroxycorticoid values the diagnosis of Addison's disease can only be made with certainty with the measurement of adrenocortical reserve by means of the standardized ACTH test.

Secondary adrenocortical insufficiency (hypopituitarism). Patients with hypopituitarism uniformly exhibit a low basal excretion of both 17-ketosteroids and 17-hydroxycorticoids. Associated deficiencies of gonadal and thyroid function are often present.

The use of ACTH in the diagnosis of adrenal insufficiency secondary to anterior pituitary insufficiency is of particular value because of the paucity of specific clinical changes referable to the adrenocortical insufficiency — for example, pigmentation and signs of electrolyte disturbance. In secondary insufficiency the response to intravenously administered ACTH is characteristically delayed in proportion to the degree and duration of the secondary adrenocortical atrophy. In contrast to the patient with Addison's disease, who shows no fall in the level of blood eosinophils and no rise in urinary 17-ketosteroids and 17-hydroxycorticoids, the patient with secondary adrenal insufficiency shows a gradual response to ACTH. In most cases a normal degree of eosinopenia and a significant rise in urinary steroid excretion occur with three to five days of intravenous ACTH infusion (Fig. 4).

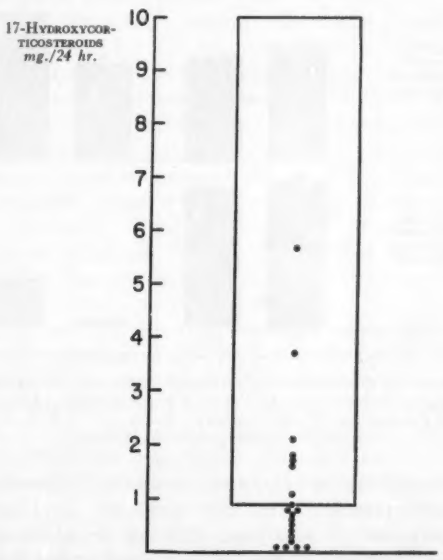


FIGURE 3. *Urinary 17-Hydroxycorticoid Excretion in 20 Patients with Untreated Addison's Disease.*
The range for normal subjects (1-10 mg. per twenty-four hours) is shown in the block.

Iatrogenic adrenocortical insufficiency. Patients who have been maintained for a prolonged period on cortisone or hydrocortisone therapy show varying degrees of diminished adrenocortical function as a result of inhibition of the secretion of ACTH from the anterior pituitary gland. Because exogenous cortisone and hydrocortisone may contribute appreciably to urinary 17-hydroxycorticoid and 17-ketosteroid levels, it is difficult to evaluate spontaneous adrenocortical secretion in such patients unless therapy is withdrawn. However, since negligible quantities of steroid are found in the urine after the administration of therapeutically effective doses of fluorohydrocortisone, it is possible to substitute this compound for cortisone or hydrocortisone (in the ratio of approximately 1 mg. of fluorohydrocortisone to 20 mg. of cortisone or hydrocortisone) while a standard ACTH test is being carried out. In this way the dangers inherent in the sudden withdrawal of corticoid therapy may be avoided, and a definitive answer regarding adrenocortical reserve may be obtained. Such a study has been carried out in a forty-six-year-old man with salt-losing nephritis who had been treated for Addison's disease with 50 mg. of cortisone per day for a period of two years (Fig. 2). It can be seen that an adequate response to ACTH was rapidly obtained after discontinuance of the cortisone while the patient was being maintained on 2 mg. of fluorohydrocortisone by mouth per day. On completion of the ACTH test the fluorohydrocortisone was discontinued. No symptoms or signs of adrenal insufficiency appeared. Indeed, normal levels of urinary 17-hydroxycorticoids were subsequently demonstrated.

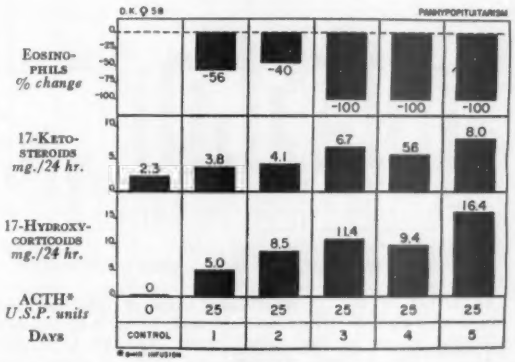


FIGURE 4. *Adrenal Response to Intravenous Administration of ACTH in a Fifty-Eight-Year-Old Woman with Panhypopituitarism.*

Diagnosis of Adrenocortical Hyperfunction

The clinical picture of adrenocortical hyperfunction extends in a broad spectrum from Cushing's

syndrome to the adrenogenital syndrome. Pure Cushing's syndrome is due to an excessive adrenocortical secretion of the 11,17-oxygenated corticoids, hydrocortisone and possibly cortisone, whereas the adrenogenital syndrome (adrenal virilism) is caused by an increased secretion of androgens from the adrenal cortex. Between these two extremes are many patients who present manifestations of each syndrome to varying degrees ("mixed syndrome"). Rarely, adrenocortical hyperfunction may involve an increased secretion of estrogens that is associated with feminization in the male.[11] Adrenocortical hyper-

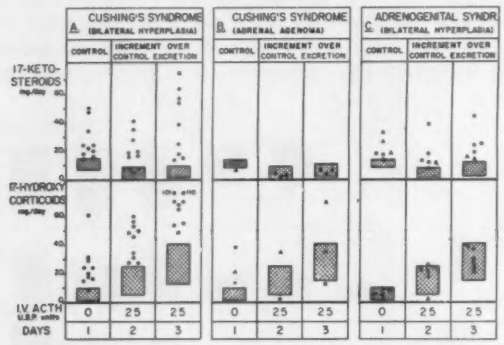


FIGURE 5. *Response to ACTH in Adrenocortical Hyperfunction.*

The blocks in the "control" day columns represent the range of values for 17-ketosteroid and 17-hydroxycorticoid excretion in the normal adult female. The blocks in the "ACTH" day columns represent the range of values, expressed as increments over control excretion, obtained with the two-day intravenous ACTH test in 40 adult hospitalized patients with no evidence of endocrine disease.

function preferentially involving the excessive secretion of aldosterone has recently been described.[12]

In patients suspected of having hyperadrenocorticism two problems in diagnosis must be considered. The first is concerned with the type of hormone excess — that is, 11,17-oxygenated corticoids (Cushing's syndrome) or androgenic steroids (adrenal virilism). An elevated resting level of urinary 17-hydroxycorticoids in the absence of an increase in the 17-ketosteroid level suggests pure Cushing's syndrome. An elevated resting level of 17-ketosteroids with a normal or low level of 17-hydroxycorticoids is found in the classic case of adrenal virilism. Increased excretion of both 17-hydroxycorticoids and 17-ketosteroids occurs in the cases of "mixed syndrome." The second diagnostic consideration in patients with hyperadrenocorticism is the nature of the lesion responsible for the increased hormone secretion. The approach to this problem, which is one of differentiation among hyperplasia, adenoma and carcinoma, has included a study of the adrenocortical response to the stimulating effect of ACTH and to the inhibiting influence of cortisone and its derivatives. It seemed reasonable to expect that the sensitivity of the steroid-producing tissue to variations in the level of circulating exogenous or endogenous ACTH might give some indication of the degree of its dependence on the anterior pituitary gland and hence its histologic characteristics.

Cushing's syndrome. Increased resting levels of urinary 17-hydroxycorticoids are usually found in association with the clinical manifestations of Cushing's syndrome (Fig. 5 and 6). However, this is not always so; indeed, in 1 patient with bilateral adrenal hyperplasia, the values before ACTH stimulation were only at the upper limit of the normal range. It is of some interest that this patient did not demonstrate the normal nocturnal decline in excretion of 17-hydroxycorticoids[13] but showed a fairly constant rate of excretion of these steroids throughout the day and night. Five other patients with Cushing's syndrome were studied in this manner. One with an adrenocortical adenoma and 3 with bilateral hyperplasia had no diurnal variation in 17-hydroxycorticoid excretion; the fourth patient, who had unilateral adrenal hyperplasia with atrophy of the contralateral gland, did demonstrate a normal diurnal variation.

Increased resting levels of 17-ketosteroids are not always found in patients with clinical evidence of

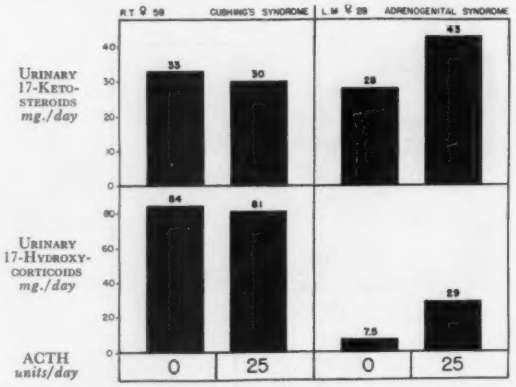


FIGURE 6. *Comparison of Adrenal Response to Administration of Intravenous ACTH in 2 Patients with Adrenocortical Carcinoma (1 with Cushing's Syndrome, and the Other with the Adrenogenital Syndrome).*

Cushing's syndrome. In our series the 17-ketosteroid excretion ranged from 13 to 50 mg. in bilateral hyperplasia (9 cases) and 7-13 mg. in adenoma (3 cases) and was 80 mg. for twenty-four hours in the 1 case of carcinoma. Forbes and Albright[14] have reported an average 17-ketosteroid value of 18.1 mg. per twenty-four hours (range, 2.1 to 40 mg.) in 37 patients with bilateral hyperplasia, 5.7 mg. (range, 1.7 to 11.9 mg.) in 18 patients with adenoma and 124 mg. (range, 1.1 to 649 mg.) in 20 patients with carcinoma. It can be seen that although in general the 17-ketosteroid values were low in adenoma, high in carcinoma and slightly elevated in bilateral hyperplasia, there was considerable overlap between the three groups. It appears that it is not easy to predict

the type of adrenal lesion in Cushing's syndrome from the basal level of 17-ketosteroids.

Recent experience, however, has indicated that a more *definitive* differentiation of the type of lesion may be obtained by measurement of the adrenocortical response to ACTH. In 10 patients with Cushing's syndrome (7 female and 3 male) who were found at operation to have bilateral adrenal hyperplasia, there was a hyperactive (exceeding the normal range) response to ACTH as measured by the rise in urinary 17-hydroxycorticoids. In addition all exhibited a hyperactive 17-ketosteroid response at least during the second twenty-four hours of stimulation (Fig. 5).

In contrast to patients with Cushing's syndrome due to hyperplasia, 3 patients (all females) with adrenal adenoma showed a *normal* 17-ketosteroid response and a variable response in 17-hydroxycorticoid excretion; in 1 there was a hypoactive, in the second a normal, and in the third a hyperactive response (Fig. 5). Since the contralateral gland in patients with Cushing's syndrome due to a unilateral adrenocortical adenoma is almost invariably atrophied, it is probable that the extent to which such patients respond to ACTH depends on the degree of autonomy of the tumor itself.

Two patients with adrenal carcinoma failed to respond to ACTH. The results obtained in 1 of these are shown on the left-hand side of Figure 6. Basal excretion of 17-ketosteroids and of 17-hydroxycorticoids was markedly elevated, but no response to ACTH was obtained. At operation the left adrenal gland contained an encapsulated tumor consisting of atypical cells interpreted as representing adrenocortical carcinoma. The contralateral gland was atrophied. A failure to respond to ACTH in Cushing's syndrome due to adrenocortical carcinoma has also been reported by Burnett et al.[15]

Jailer and his associates[16] recently reported that the administration of 200 mg. of cortisone per day for three to five days by intramuscular injection produced a significant fall in urinary 17-ketosteroid levels in 5 patients with Cushing's syndrome due to bilateral adrenal hyperplasia. No decrease in 17-ketosteroid excretion was observed when the hormone was given to 5 patients with adrenocortical tumor. We have carried out similar studies in 5 patients with Cushing's syndrome due to bilateral hyperplasia. After either cortisone or hydrocortisone had failed to produce a fall in urinary 17-ketosteroids in the first patient, the remaining 4 were given fluorohydrocortisone. Three patients were given 5 mg. of this compound by mouth twice daily for four days, and the fourth was given 25 mg. by mouth daily for three days. In none of these patients was it possible to demonstrate a significant decrease in either 17-ketosteroid or 17-hydroxycorticoid excretion (Fig. 7). It is to be pointed out that the daily doses of this compound used are approximately equivalent to 200 to 400 mg. of cortisone in terms of their ability to inhibit the secretion of ACTH from the anterior pituitary gland.[5] Moreover, the duration of action of orally administered fluorohydrocortisone is as great as that of cortisone given by intramuscular injection. It thus appears at present that the inhibition test with cortisone or fluorohydrocortisone may be less reliable than the ACTH test for the differentiation of the lesions that may be responsible for a state of Cushing's syndrome.

It is appreciated that these findings regarding ACTH and cortisone or fluorohydrocortisone tests apply not only to Cushing's syndrome in the classic form but also to the "mixed syndrome" in which

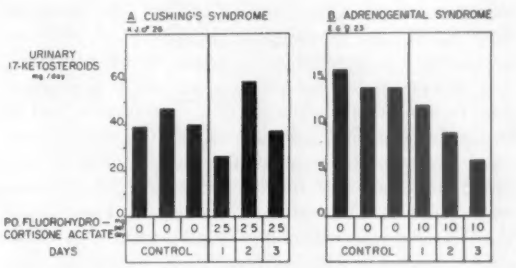


FIGURE 7. *Effect of Fluorohydrocortisone Administration in 2 Patients with Bilateral Adrenocortical Hyperplasia (1 with Cushing's Syndrome, and the Other with the Adrenogenital Syndrome).*

there are also signs of virilization and elevation of both 17-ketosteroid and 17-hydroxycorticoid excretion.

Adrenogenital syndrome (adrenal virilism). In contrast to Cushing's syndrome, in which the adrenal cortex is the mediator of the disturbance, a syndrome characterized by virilization in the female may be caused by a lesion in either the adrenal cortex or the ovary. The former may be bilateral hyperplasia, adenoma or carcinoma. The ovarian lesions include arrhenoblastoma and Leydig-cell tumor. Functioning "adrenal-rest" tumors have been found in the ovary and elsewhere in the abdominal cavity outside the normal site of the adrenal cortex.[17,18] No studies of steroid excretion after the administration of ACTH or cortisone in such cases have been reported.

In 6 adult females with evidence of virilization but no signs of Cushing's syndrome normal levels of 17-hydroxycorticoids and elevated levels of 17-ketosteroids were found. The 17-hydroxycorticoids showed a normal response to ACTH stimulation, whereas a hyperactive response as measured by the rise in 17-ketosteroid excretion was observed (Fig. 5).

In contrast to the lack of response to inhibitory doses of cortisone or fluorohydrocortisone in the patients with Cushing's syndrome, the administration of these compounds to each of the 6 patients exhibiting virilization led to a dramatic fall of 17-ketosteroid excretion to normal levels or below. The

effectiveness of orally administered fluorohydrocortisone in 1 of these patients is demonstrated in Figure 7.

The ovaries were explored in each case, and in none was a tumor discovered. Because of the hyperactive 17-ketosteroid response to ACTH and the profound fall of 17-ketosteroid excretion in response to cortisone or fluorohydrocortisone administration, it was considered unlikely that these patients had adrenocortical tumors, and exploration of the adrenal glands has not been carried out. Four of the 6 patients have now been maintained for six to twelve months on suppressive doses of fluorohydrocortisone. Clinical improvement has been observed in 3, and in the fourth the disease has not progressed. Thus, although an anatomic diagnosis has not been made in these cases, the presumptive diagnosis of bilateral adrenocortical hyperplasia appears to be justified.

A twenty-eight-year-old woman with virilization due to unilateral adrenocortical carcinoma had a high 17-ketosteroid but a normal 17-hydroxycorticoid excretion; she responded to ACTH (Fig. 6) but failed to respond to the administration of cortisone with a fall in 17-ketosteroid excretion. The finding that in adrenal virilism the administration of cortisone to patients with adrenocortical tumor, in contrast to those with hyperplasia, fails to cause a fall in 17-ketosteroid excretion has been described previously by Wilkins,[19] Bartter et al.[20] and Jailer and his associates.[16]

It is our policy in cases of the virilizing syndrome to follow the urinary 17-ketosteroid excretion during the two-day intravenous ACTH test and during the administration of fluorohydrocortisone acetate by mouth in a dose of 10 to 25 mg. per day for five days. When a hyperactive 17-ketosteroid response to ACTH is observed in association with a clear-cut fall of 17-ketosteroid excretion during fluorohydrocortisone administration the lesion is assumed to be bilateral adrenal hyperplasia. When such responses to ACTH and fluorohydrocortisone do not occur, it is assumed that the lesion is either an adrenocortical or an ovarian tumor. In the absence of localizing evidence of adrenocortical tumor the relatively simple operation of pelvic laparotomy is first performed. In the absence of a responsible ovarian lesion the adrenal glands are then explored.

Theoretical Considerations

On the basis of the findings mentioned above, certain points may be made regarding the pathogenesis of adrenal hyperfunction. It is generally agreed that the manifestations of both Cushing's syndrome and the adrenogenital syndrome are due to excessive adrenocortical secretion. Whether this hypersecretion is the result of a primary disturbance in the hypothalamus, the anterior pituitary gland or the adrenal gland itself has been a subject of debate for some time. In patients in whom an adrenal adenoma or carcinoma has been demonstrated it has been considered that the gland is the primary site of origin of the disease, although, until more is known about the factors that initiate adrenal tumor growth, even this assumption is in doubt. It is in the cases in which bilateral adrenocortical hyperplasia has been found that there has been the greatest difference of opinion. For example, bilateral hyperplasia in Cushing's syndrome may be due to increased ACTH secretion from the anterior pituitary gland or to an inherent abnormality in the adrenal glands, or to both. As shown by the studies reported here, such patients exhibit a hyperactive response to ACTH. However, patients with normal adrenal glands who have received a long course of ACTH gel therapy, with rises in the urinary 17-hydroxycorticoids to levels found in Cushing's syndrome, do not show a hyperactive response to the two-day intravenous ACTH test.[21] This finding suggests that the adrenal dysfunction in Cushing's syndrome due to bilateral hyperplasia cannot be caused solely by an increased ACTH secretion. It is possible, however, that an increased output of a pituitary factor such as that described by Liddle et al.[22] is responsible for the adrenal disturbance in Cushing's syndrome. Although the administration of this substance to normal subjects did not lead to an increase in secretion of adrenal steroids, it did alter the glands in such a way that they responded in a hyperactive manner to exogenous ACTH.

Whereas the evidence favoring a primary adrenal dysfunction in Cushing's syndrome due to bilateral hyperplasia is suggestive only, there is strong support for the concept of adrenal primacy in *infants* with adrenal virilism due to bilateral hyperplasia. Dorfman[23] has obtained evidence that in these patients there is a deficiency of certain of the adrenal enzymes (for example, 21-hydroxylase) required for the synthesis of hydrocortisone. These infants show elevated 17-ketosteroid but low to absent 17-hydroxycorticoid excretion. In *adult* females with adrenal virilism and bilateral hyperplasia it is uncommon, however, to find a diminished 17-hydroxycorticoid excretion. Five of the six patients with this condition in our series had normal urinary 17-hydroxycorticoid levels (Fig. 5). It is of interest that 2 of these had clinical evidence of hyperpituitarism — that is, acromegaly and galactorrhea. It is possible, then, that in certain adult cases of adrenal virilism with bilateral hyperplasia there is a primary disturbance in the anterior pituitary gland.

Because of the small number of cases involved in our series one cannot be certain that future studies of patients with hyperadrenocorticism will confirm the findings described. For example, it is conceivable that an adrenocortical carcinoma will be discovered that responds to ACTH stimulation. A somewhat analogous situation has been found in certain cases of thyroid carcinoma in which the metastases have

been induced to increase their radioactive iodine uptake after the administration of pituitary thyrotrophin.[24] A further point must be considered. The response to ACTH of a patient with an adrenocortical carcinoma depends not only on the response of the carcinoma itself but also on that of the contralateral gland. In Cushing's syndrome due to unilateral adrenal carcinoma with increased 17-hydroxycorticoid secretion one anticipates secondary atrophy of the opposite gland. Under these circumstances one expects little response to the two-day intravenous ACTH test unless the carcinoma itself responds. In adrenal virilism due to carcinoma with an increased androgen secretion one anticipates that the contralateral gland will show little atrophy and may therefore respond to ACTH. These considerations are borne out by the findings shown in Figure 6. Thus, it may be stated that whereas a significant response to ACTH in adrenal virilism does not necessarily rule out the presence of an adrenal carcinoma, such a response is unlikely to occur when a carcinoma is the cause of Cushing's syndrome.

It should be remembered that 17-hydroxy-11-desoxycorticosterone (Reichstein's compound S) is a 17-hydroxycorticoid and is therefore measured by the method used. Although this compound does not appear to be secreted in appreciable amounts by the normal human adrenal cortex Dohan et al.[25] have recently reported its increased excretion in a patient with adrenocortical carcinoma. Since compound S, unlike hydrocortisone, has little glucocorticoid or mineralocorticoid activity and is a weak inhibitor of ACTH secretion,[26] one would expect an increased excretion of 17-hydroxycorticoids without a clinical picture of Cushing's syndrome in the presence of an increased secretion of this compound. Furthermore, if the secreting tumor were a unilateral one, the opposite adrenal gland would not be atrophied and would therefore respond to ACTH.

Conclusions

In all cases of disturbed adrenocortical function (whether above or below normal) the final diagnosis will be made on the basis of all the information obtained from an accurate history and physical examination and appropriate x-ray and laboratory studies. However, when one suspects adrenocortical dysfunction it is important to investigate the nature and quantities of the adrenal secretory products if a definitive diagnosis is to be established. Standardized technics for carrying out this approach have been described. They are not the only methods available nor necessarily the best. They are practical, however, and they have proved their usefulness.

We are indebted to the following organizations for providing material used in these studies: the Armour Laboratories, Chicago, Illinois, for ACTH; Merck and Company, Incorporated, Rahway, New Jersey, for cortisone; the Squibb Institute for Medical Research, New Brunswick, New Jersey, for fluorohydrocortisone; and the Upjohn Company, Kalamazoo, Michigan, for ACTH.

References

1. Nelson, D. H., and Samuels, L. T. Method for determination of 17-hydroxycorticosteroids in blood: 17-hydroxycorticosterone in peripheral circulation. *J. Clin. Endocrinol.* **12**:519-526, 1952.
2. Reddy, W. J. Modification of Reddy-Jenkins-Thorn method for estimation of 17-hydroxycorticoids in urine. *Metabolism* **3**:489-492, 1954.
3. Eik-Nes, K., Sandberg, A. A., Nelson, D. H., Tyler, F. H., and Samuels, L. T. Changes in plasma levels of 17-hydroxycorticosteroids during intravenous administration of ACTH. I. Test of adrenocortical capacity in human. *J. Clin. Investigation* **33**: 1502-1508, 1954.
4. Jenkins, D., Forsham, P. H., Laidlaw, J. C., Reddy, W. J., and Thorn, G. W. Use of ACTH in diagnosis of adrenal cortical insufficiency. *Am. J. Med.* **18**:3-14, 1955.
5. Goldfien, A., Laidlaw, J. C., Abu Haydar, N., Renold, A. E., and Thorn, G. W. Fluorohydrocortisone and chlorohydrocortisone, highly potent derivatives of compound F. *New Eng. J. Med.* **252**: 415-421, 1955.
6. Drekter, I. J., et al. Determination of urinary steroids. I. Preparation of pigment-free extracts and simplified procedure for estimation of total 17-ketosteroids. *J. Clin. Endocrinol.* **12**:55-65, 1952.
7. Holtorff, A. F., and Koch, F. C. Colorimetric estimation of 17-ketosteroids and their application to urine extracts. *J. Biol. Chem.* **135**:377-392, 1940.
8. Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G. Clinical studies with pituitary adrenocorticotropin. *J. Clin. Endocrinol.* **8**:15-66, 1948.
9. Abu Haydar, N., Reddy, W. J., and Thorn, G. W. Unpublished data.
10. Perkoff, G. T., Sandberg, A. A., Nelson, D. H., and Tyler, F. H. Clinical usefulness of determination of circulating 17-hydroxycorticosteroid levels. *Arch. Int. Med.* **93**:1-8, 1954.
11. Wilkins, L. Feminizing adrenal tumor causing gynecomastia in boy of five years contrasted with virilizing tumor in five-year-old girl: classification of seventy cases of adrenal tumor in children according to their hormonal manifestations and review of eleven cases of feminizing adrenal tumor in adults. *J. Clin. Endocrinol.* **8**:111-132, 1948.
12. Conn, J. W. Primary aldosteronism, new clinical syndrome. *J. Lab. & Clin. Med.* **45**:3-17, 1955.
13. Laidlaw, J. C., Jenkins, D., Reddy, W. J., and Jakobson, T. Diurnal variation in adrenocortical secretion. *J. Clin. Investigation* **33**:950, 1954.
14. Forbes, A. P., and Albright, F. Comparison of 17-ketosteroid excretion in Cushing's syndrome associated with adrenal tumor and with adrenal hyperplasia. *J. Clin. Endocrinol.* **11**:926-935, 1951.
15. Burnett, R., Rukes, M., Kolb, F., and Forsham, P. H. Functional diagnosis of different states of adrenocortical hyperactivity. *J. Clin. Endocrinol.* **14**:775, 1954.
16. Jailer, J. W., Gold, J. J., and Wallace, E. Z. Evaluation of cortisone test as diagnostic aid in differentiating adrenal hyperplasia from adrenal neoplasia. *Am. J. Med.* **16**:340-345, 1954.
17. Kepler, E. J., and Locke, W. Adrenals. I. Chronic adrenal hyperfunction. In *Textbook of Endocrinology*. Edited by R. H. Williams and P. H. Forsham. 793 pp. Philadelphia: Saunders, 1950. Pp. 180-247.
18. Pedersen, J. Virilizing ovarian tumors. *J. Clin. Endocrinol.* **7**:115-129, 1947.
19. Wilkins, L. Diagnosis of adrenogenital syndrome and its treatment with cortisone. *J. Pediat.* **41**:860-874, 1952.
20. Bartter, F. C., et al. Effects of adrenocorticotropic hormone and cortisone in adrenogenital syndrome associated with congenital adrenal hyperplasia: attempt to explain and correct its disordered hormonal pattern. *J. Clin. Investigation* **30**:237-251, 1951.
21. Reddy, W. J., and Laidlaw, J. C. Unpublished data.
22. Liddle, G. W., Island, D., Rinfret, A. P., and Forsham, P. H. Factors enhancing response of human adrenal to corticotropin: is there adrenal growth factor? *J. Clin. Endocrinol.* **14**:839-858, 1954.
23. Dorfman, R. I. Metabolism of adrenal steroids. In *Adrenal Cortex. Transactions of the Fifth Conference, November 4, 5 and 6, 1953, Princeton, New Jersey*. Edited by E. P. Ralli. 187 pp. New York: Josiah Macy, Jr., Foundation, 1954. Pp. 27-96.
24. Rawson, R. W. Endocrinology of neoplastic disease. *Recent Prog. in Hormone Research* **11**:257-290, 1955.
25. Dohan, F. C., Touchstone, J. C., and Richardson, E. M. Effect of ACTH and pathological increases in adrenal cortical function on urinary alpha-ketolic steroid metabolites. *J. Clin. Investigation* **34**:485-499, 1955.
26. Thorn, G. W., et al. Pharmacologic aspects of adrenocortical steroids and ACTH in man. *New Eng. J. Med.* **248**:232-245, 284-294, 323-337, 369-378, 414-423, 588-601 and 632-646, 1953.

BLOOD LEVELS FROM ORALLY ADMINISTERED PENICILLINS G AND V*

Relation to Food Intake

WILFRED F. JONES, JR., M.D.,† AND MAXWELL FINLAND, M.D.‡

BOSTON

SEVERAL natural penicillins develop during fermentation and differ by the side chain attached through the acid amide linkage to the thiazolidine-beta-lactam skeleton of the penicillin molecule. If the concentration of the appropriate organic acid precursor is increased in the nutrient medium, the equilibrium regarding the types of penicillin produced may be shifted in favor of the type with this particular organic acid side chain. Similarly, the provision of new precursors can lead to the biosynthesis by the Penicillium mold of entirely new penicillins[1] that may have pharmacologic and physicochemical properties quite different from those of benzylpenicillin (penicillin G), and may have an altered antibacterial activity in vitro. One such product is phenoxymethylpenicillin[2-7] (penicillin V), which is notable for its high stability at pH ranges below 3.0, its low solubility in an acid medium and its easy conversion to a water-soluble (and hence probably more absorbable) alkali salt at a neutral or alkaline pH. These physical properties suggested a possible superiority of penicillin V over penicillin G for oral administration.[4-6]

A carefully controlled study was undertaken to determine the levels of penicillin activity demonstrable in plasma after oral doses of penicillin V as compared with those found after similar doses of penicillin G. In previous studies, the effects of food on the absorption of penicillin and the effects of buffers were emphasized,[8-11] and the rate of disintegration of the tablets in the stomach was also shown to have a significant role[11]; these aspects, therefore, were also considered in the present investigation.

MATERIALS AND METHODS

The subjects were 6 normal adult men, twenty-five to thirty-five years old, weighing between 155 and 190 pounds (average, 175 pounds). In each experiment each subject received a single tablet containing 200,000 units of penicillin as one of the following§:

TABLET	LOT NUMBER	DISINTEGRATION TIME IN ARTIFICIAL GASTRIC JUICE
Potassium penicillin G, unbuffered	L-3074	18 minutes
Potassium penicillin G, buffered	5A83986	21 minutes
Penicillin V ("slow")	L-3046-2	20 minutes
Penicillin V ("fast")	L-3046B-1	4½ minutes

The tablets were given either half an hour before breakfast or half an hour after breakfast, and were given on only two days a week so that at least three days elapsed between successive experiments in the same subject.

The experiments were conducted so that each subject acted as his own control. Experiments 1 to 6 were carried out simultaneously. On the first day 2 subjects received unbuffered potassium penicillin G, 1 of them before (Experiment 1) and the other after (Experiment 2) breakfast; 2 other subjects received buffered potassium penicillin G, 1 of them before (Experiment 3) and the other after (Experiment 4) breakfast; the 2 other subjects received the slowly disintegrating preparation of penicillin V, 1 of them before (Experiment 5) and the other after (Experiment 6) breakfast. This was repeated with rotation of the subjects until each subject participated in each experiment and with all 6 experiments being run each time. The more rapidly disintegrating tablets of penicillin V were supplied later; at that time 5 of the same subjects were still available. Some of them, chosen at random, received this preparation before (Experiment 7) and the others after (Experiment 8) breakfast on the next test day; the experiment was repeated later, with the subjects reversing the relation of the dose to the meal.

Citrated venous blood samples were obtained immediately before each dose (0 hours) and one, two, four and six hours after the dose. The plasma was separated promptly and stored in a refrigerator at −5°C. until all the samples were collected for that

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Aided by a grant from the United States Public Health Service.

†Assistant in medicine, Harvard Medical School; research fellow in medicine, Thorndike Memorial Laboratory.

‡Associate professor of medicine, Harvard Medical School; chief, Fourth Medical Service, Boston City Hospital; associate director, Thorndike Memorial Laboratory.

§The unbuffered potassium G and both penicillin V preparations were generously supplied by Dr. Edward F. Roberts, of Wyeth Laboratories, Philadelphia, and the buffered penicillin G tablets ("Pentids") by E. R. Squibb and Sons, New York City. We are also indebted to Dr. Roberts for making available unpublished data and pertinent literature on penicillin V, as well as the results of tests of the disintegration time of each of the tablets used in this study.

day; assays were then done on the same day, using *Streptococcus 98* as the test organism. Part of each sample was stored at −20°C., and at a later date each day's samples were again assayed, *Staphylococcus aureus 209P** being used as the test organism. Penicillin assays were carried out† by the serial twofold-dilution method in brain-heart infusion broth (Difco, pH 7.4±), 0.5 cc. of a 10^{-4} dilution of the fully grown culture of the test organism being added to an equal volume of the plasma dilutions. Endpoints were read as the maximum dilution of plasma that gave complete gross inhibition of the test organism after incubation for twenty-four hours at 37°C. When the next higher twofold dilution showed marked but incomplete inhibition (faintly discernible growth), the endpoint was expressed as one-half dilution more than that with complete inhibition. Values for penicillin concentration in the plasma samples were calculated from assays of the test strains using standard solutions of penicillin G and V that were run simultaneously; these concentrations were then calculated for each kind of penicillin (G and V) and for each test organism (*Str. 98* and *Staph. aureus 209P*) employed in the standards.

*Provided by Donald C. Grove, Division of Antibiotics, Food and Drug Administration.

†With the assistance of Ann Najarian and Clare Wilcox.

Results

Levels of Antistreptococcal Activity in Plasma

Comparisons of the levels of penicillin in plasma after the administration of any given amount when levels are expressed in terms of units or micrograms of penicillin must necessarily reflect the relative activity of the antibiotic against the assay organisms used. This results from the fact that the amount (or concentration) of penicillin required to inhibit the assay organism depends on the species or even the strain used in the test, and this, in turn, may vary with the kind of penicillin used. A more suitable comparison of the blood level after administration of various preparations of penicillin would be based on the amount of plasma required to inhibit a given test strain, and this may be expressed as the maximum dilution of the plasma that will inhibit that strain. This method of comparison was therefore chosen as offering the best way to demonstrate the relative penicillin activity of plasma after ingestion of the different tablets that were investigated.

The results of the tests carried out with *Str. 98* on the plasmas of each of the 6 subjects obtained after each of the tablets are shown in Figure 1. Each pair of panels shows all the results in 1 subject — the one of the left showing the levels of antistreptococcal ac-

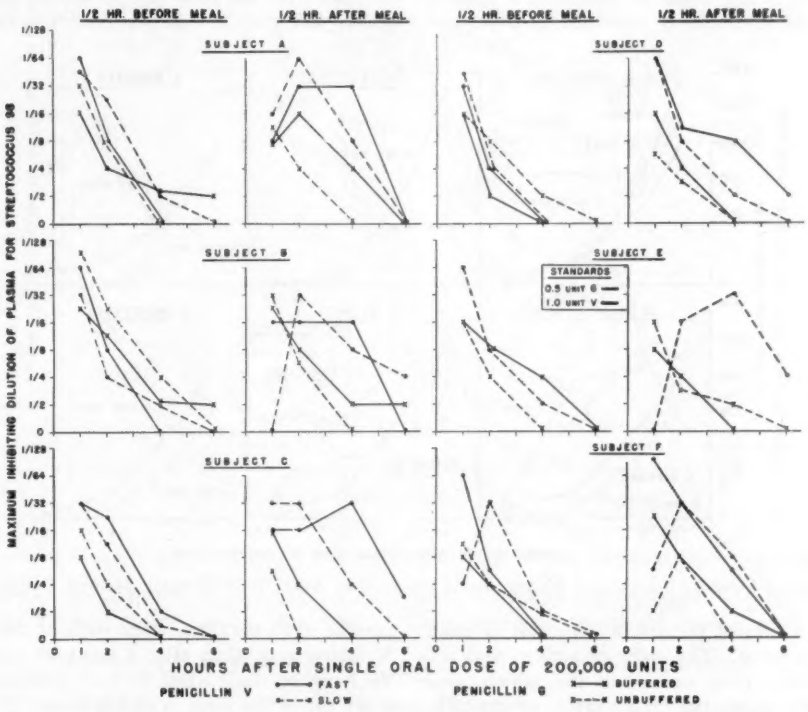


FIGURE 1. *Levels of Penicillin in Plasma after a Single Oral Dose (Broth-Dilution Method Employing* Str. 98*).*

tivity of plasma obtained when the tablets were taken before breakfast, and that on the right the corresponding levels resulting from the tablets taken after breakfast. Considerable individual variations in the levels and duration of penicillin activity resulted from each of the tablets, both before and after breakfast. However, for most of the subjects, the relative levels of antistreptococcal activity were similar. When taken before breakfast, the slowly disintegrating tablet of penicillin V gave the best results; the rapidly disintegrating tablet of penicillin V ranked second, and the unbuffered penicillin G next, and 4 preparations quite clearly, the rapidly disintegrating tablet of penicillin V showing the highest and most prolonged levels, and the slower tablet of penicillin V ranking second in this respect, but showing much greater activity than either tablet of penicillin G; the superior levels of the buffered as compared with the unbuffered tablet of penicillin G taken after the meal are also apparent.

The comparisons of the average levels of antistreptococcal activity obtained with each preparation in relation to the meal are shown in the remaining panels of Figure 2. The striking superiority of the

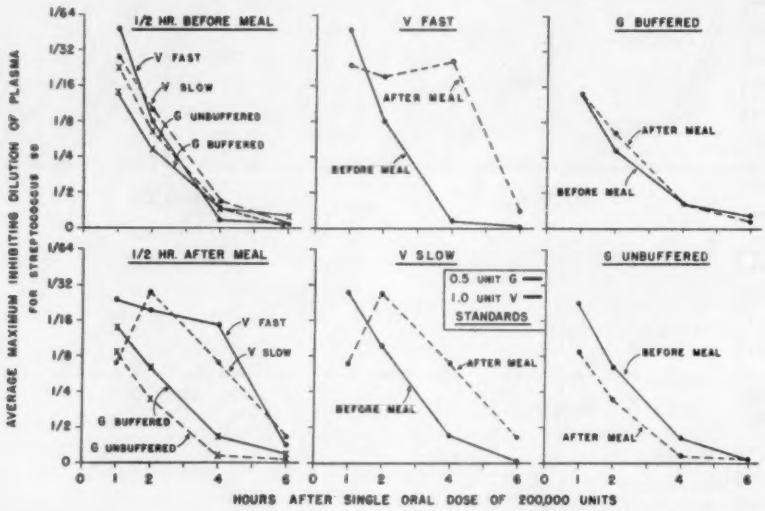


FIGURE 2. *Average Levels of Penicillin in Plasma after a Single Oral Dose (Broth-Dilution Method Employing* Str. 98*).*

the buffered tablet of potassium penicillin G made the poorest showing. The order of activity was different and more clear cut when the tablets were taken after the meal; the "fast" tablet of penicillin V was definitely superior to the others, the "slow" tablet of V ranked second, the buffered penicillin G ranked third, and the unbuffered tablet of penicillin G was definitely inferior to all the others. The only deviation from this order was in subject E, who showed slightly better levels with the unbuffered than with the buffered penicillin G; this subject was not available for the experiments with the fast penicillin V tablets.

The average levels of antistreptococcal activity in the plasma of these subjects are shown in Figure 2. The upper panel on the left depicts the average levels for the tablets taken before breakfast, and those in the lower left panel the corresponding levels for the tablets taken after breakfast. The average values for the pre-meal tests are quite similar for all 4 preparations although they do show the relative order of activity already noted for most of the individual subjects. The average values for the tests done after the meal, however, depict the differences among the plasma levels obtained when each of the 2 penicillin V tablets was taken after a meal, as compared with the levels resulting when the corresponding tablet was taken before the meal, is clearly shown. There was no significant difference in the average levels resulting from the buffered penicillin G tablets in relation to the meal, but the levels obtained with the unbuffered tablets of penicillin G were definitely inferior when they were taken after breakfast.

Levels of Antistaphylococcal Activity*

The results obtained when the same samples of plasma were tested for activity against *Staph. 209P* are shown in Figures 3 and 4. On the whole, these levels were slightly higher than the corresponding ones obtained with *Str. 98*, reflecting the greater activity of the plasma against the staphylococcus, regardless of which tablet had been taken. However, the relative activity of the plasmas obtained from each subject after each of the 4 tablets was essentially the same, both before and after the meal, as was previously noted for antistreptococcal activity; the same was true for the average levels as shown in Figure 4.

*A few of the specimens were no longer available for these tests.

Concentrations of Penicillin in Plasma Expressed in Terms of Penicillins G and V

As already indicated, the values for the concentration of penicillin in plasma depend on the sensitivity of the test strain to the 2 forms of penicillin. The sensitivity of the 2 assay strains used in this study, when tested with standard solutions of the 2 forms of penicillin prepared from dried powders, is shown in the lower portion of Table 1; alongside these results are listed the corresponding values for the minimum detectable concentrations in plasma (marked inhibition in 0.5 cc. of the citrated plasma). These values represent the means of the results of repeated tests, but there was remarkable uniformity

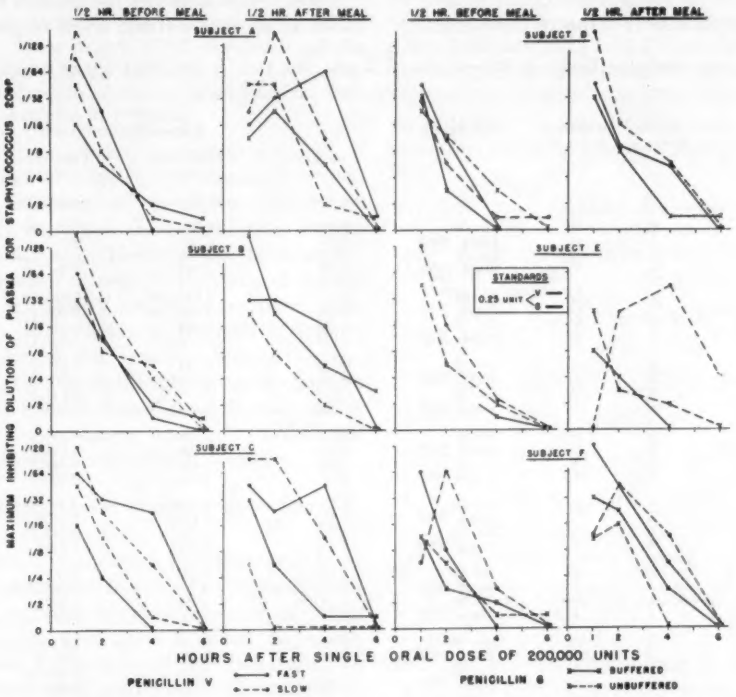


FIGURE 3. *Levels of Penicillin in Plasma after a Single Oral Dose (Broth-Dilution Method Employing* Staph. 209P).

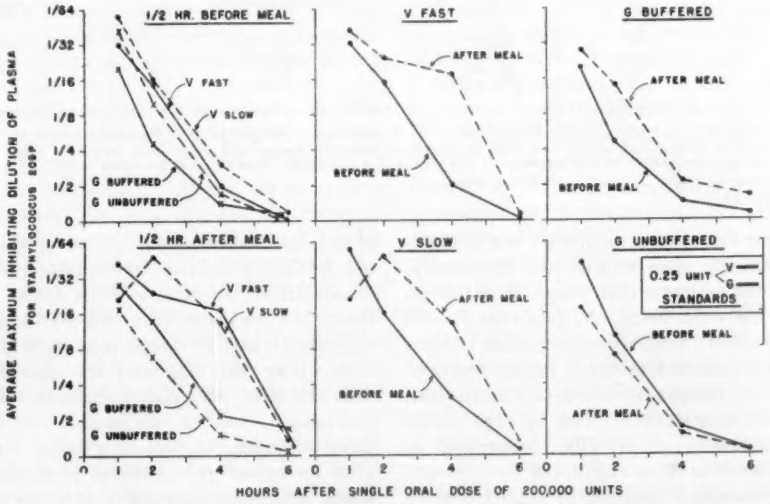


FIGURE 4. *Average Levels of Penicillin in Plasma after a Single Oral Dose (Broth-Dilution Method Employing* Staph. 209P).

in these results from one test to another, with only minor discrepancies, usually representing a single two-fold dilution or less.

Because the staphylococcus was more sensitive than the streptococcus to both penicillins G and V, the activity of the plasmas in terms of micrograms of strains, are given in Table 1. These values, of course, show the relations already noted in Figures 1-4.

Delay in Absorption and Duration of Penicillemia

Table 1 also indicates the number of subjects who failed to show detectable levels of penicillin at each

TABLE 1. *Average Penicillin Levels in Plasma after a Single Oral Dose of 200,000 Units of Penicillin G or V.**

Experiment No.	Penicillin Tablet	No. of Subjects	Penicillin Standard	Test Strain	Average Concentration†			
					1 hr. after dose‡	2 hr. after dose	4 hr. after dose	6 hr. after dose
					microgm./cc.	*microgm./cc.*	*microgm./cc.*	*microgm./cc.*
1	G,	6	G	*Str. 98*	0.202	0.059	0.015(3)	0
	unbuffered	6	G	*Staph. 209P*	0.267	0.062	0.010	0.007(5)
	before	6	V	*Str. 98*	0.575	0.166	0.041(3)	0
	meal	6	V	*Staph. 209P*	0.188	0.044	0.007	0.005(5)
2	G,	6	G	*Str. 98*	0.077	0.031(1)	0.010(5)	0
	unbuffered	5	G	*Staph. 209P*	0.108	0.044(1)	0.009(2)	0.007(4)
	after	6	V	*Str. 98*	0.218	0.089(1)	0.039(5)	0
	meal	5	V	*Staph. 209P*	0.077	0.031(1)	0.007(2)	0.005(4)
3	G,	6	G	*Str. 98*	0.124	0.041	0.015(3)	0.012(4)
	buffered	6	G	*Staph. 209P*	0.125§	0.029§	0.009(2)	0.007(4)
	before	6	V	*Str. 98*	0.354	0.117	0.041(3)	0.031(4)
	meal	6	V	*Staph. 209P*	0.088§	0.021§	0.007(2)	0.005(4)
4	G,	6	G	*Str. 98*	0.124	0.059	0.015(3)	0.010(5)
	buffered	6	G	*Staph. 209P*	0.176	0.088	0.014(1)	0.010§(2)
	after	6	V	*Str. 98*	0.354	0.166	0.041(3)	0.029(5)
	meal	6	V	*Staph. 209P*	0.125	0.062	0.009(1)	0.007§(2)
5	V,	6	G	*Str. 98*	0.251	0.088	0.015(1)	0
	slow	6	G	*Staph. 209P*	0.353	0.101§	0.020§	0.007§(4)
	before	6	V	*Str. 98*	0.709	0.251	0.043(1)	0
	meal	6	V	*Staph. 209P*	0.251	0.071§	0.014§	0.005§(4)
6	V,	6	G	*Str. 98*	0.060(2)	0.251	0.062	0.015(4)
	slow	5	G	*Staph. 209P*	0.133(1)	0.306	0.083	0.008(4)
	after	6	V	*Str. 98*	0.170(2)	0.709	0.177	0.041(4)
	meal	5	V	*Staph. 209P*	0.094(1)	0.217	0.059	0.006(4)
7	V,	5	G	*Str. 98*	0.435	0.071	0.010(4)	0
	fast	5	G	*Staph. 209P*	0.202	0.094	0.013(3)	0
	before	5	V	*Str. 98*	1.232	0.204	0.039(4)	0
	meal	5	V	*Staph. 209P*	0.144	0.067	0.009(3)	0
8	V,	5	G	*Str. 98*	0.218	0.177	0.133	0.013(3)
	fast	5	G	*Staph. 209P*	0.267	0.153	0.108	0.007(4)
	after	5	V	*Str. 98*	0.618	0.500	0.380	0.036(3)
	meal	5	V	*Staph. 209P*	0.189	0.108	0.077	0.005(4)

		Minimum Inhibiting Concentration	Minimum Detectable Concentration in Plasma
G	*Str. 98*	0.0078	0.013
G	*Staph. 209P*	0.0055	0.090
V	*Str. 98*	0.022	0.036
V	*Staph. 209P*	0.0039	0.063

*Values based on assays done in broth with *Str. 98* or *Staph. 209P* & calculated by comparison with standard solutions of penicillins G or V.

†Calculated from mean of dilution endpoints for all available samples. Those with undetectable levels were assigned a value 0; the numbers of such subjects are shown in parentheses. An average value of 0 indicates that all samples failed to show detectable levels.

‡Blood obtained before every dose, & this level in every instance 0.

§One sample not available.

the corresponding forms of penicillin do not fully reflect the fact that the plasmas inhibited the staphylococcus in greater dilutions than they did the streptococcus. On the other hand, the fact that *Str. 98* was considerably more sensitive to penicillin G than to penicillin V is reflected in much higher levels of penicillin V in the plasma, in terms of micrograms, when tested with this strain.* The average values for the concentrations of penicillin, expressed in terms of penicillin G or V as calculated by comparisons with corresponding controls of standard solutions of the 2 forms of penicillin and with the 2 test of the intervals studied. None of the subjects had any inhibitory activity for either test organism in the bloods drawn before any of the doses. As seen from this table, and also from Figures 1 and 3, only 2 subjects (B and F) failed to show a detectable level at one hour; this was after the postcibal dose of the slow tablet of penicillin V in both. By the end of two hours, 1 subject (C) already had less than a detectable amount of penicillin in the plasma; this was after an unbuffered tablet of penicillin G. At four hours, a varying number of subjects failed to show any detectable penicillin activity with each of the penicillin G tablets, taken both before and after breakfast, and with the fast penicillin V taken before

*The same fact, of course, is true when the values are expressed in units, 1 unit being equivalent to about 0.6 microgm. of either form.

that meal; this occurred more frequently when *Str. 98* was used as the assay organism. All subjects had detectable levels in the plasma at four hours when either of the penicillin V tablets was taken after the meal. Most of the subjects no longer had any detectable level of penicillin when tested at six hours with either *Str. 98* or *Staph. 209P*, regardless of the preparation or the relation to meals.

Total Penicillin Activity in Plasma

To obtain a comparative numerical estimate of the total penicillin activity in the plasma that each subject derived from each of the tablets, the "areas" subtended by the curves of the penicillin levels were calculated (Table 2). These values confirm the greater total amounts of penicillin activity of plasma resulting from penicillin V tablets as compared with those obtained with penicillin G; the greater activity derived from each of the penicillin V tablets taken after breakfast as compared with that produced with the same tablets taken before the meal; and, finally, the poorer activity resulting from the unbuffered tablet of penicillin G taken after breakfast.

Preliminary Observations on Blood Levels during Treatment

Three patients, 2 with acute pneumococcal lobar pneumonia of moderate severity but without bacteremia and 1 with asymptomatic hemolytic streptococcal pharyngitis, were given 2 tablets of penicillin V followed by 1 tablet every four hours for two and a half to three and a half days. Lot 3046B-2, the "slow" tablet, was used in the first 2 and Lot 3046B-1, the "fast" tablet, was used in the third. The patients with pneumonia became afebrile and symptom free in about twenty-four hours, after which pneumococci were cleared from the sputum, and the streptococci could not be cultured from the sputum of the third patient after treatment was begun.

Blood for penicillin assays was obtained before the first dose and before each of 6 to 10 later doses in the first 2 patients, and the plasma stored at −20°C. until all had been collected; they were then assayed at the same time with *Str. 98*. In terms of the penicillin V standard, levels of 0.5 to 2.0 units were maintained throughout in the first patient; this corresponded to levels of 0.25 to 1.0 units in terms of the penicillin G standard that was run at the same time. In the second patient, the levels ranged irregularly from 0.06 to 1.0 microgm. per cubic centimeter calculated as penicillin V and correspondingly lower levels in terms of penicillin G.

In the third patient, 10 samples of blood were drawn at intervals of one to three and a half hours after different doses, and they were all assayed simultaneously with both *Str. 98* and *Staph. 209P* and calculated by comparisons with standard solutions of both penicillin G and V. The staphylococcus in these tests was twice as sensitive (that is, inhibited in one higher dilution) as the streptococcus to penicillin G and four times as sensitive to penicillin V; the streptococcus was four times, and the staphylococcus twice as sensitive to G as to V. When tested with *Str. 98*, the plasma levels in this patient ranged from less than 0.015 to 0.25 microgm. per cubic centimeter calculated as penicillin G, and from less than 0.12 to 1.0 microgm. per cubic centimeter calculated as penicillin V. When tested with *Staph. 209P*, the same samples yielded levels ranging from 0.02 to 0.25 microgm. per cubic centimeter, calculated as penicillin G, and from 0.04 to 0.5 microgm. calculated as penicillin V.

TABLE 2. *Total Penicillin Activity of Plasma after Single Oral Doses.*

Penicillin Tablet	Relation to Meal	No. of "Dilution-Hours" of Penicillin Activity*			
		against *Str. 98*		against *Staph. 209P*	
		Range	Mean	Range	Mean
G, unbuffered	Before	7-17	10	9½-19	12½
	After	2½- 8½	6	2½-16½	10
G, buffered	Before	4½-13½	9	7-13½	9½
	After	6-13	9½	6-22	13½
V, slow	Before	8½-14	11½	10½-18½	15
	After	15½-21½	17	18½-23	21
V, fast	Before	8-14	10½	10½-22½	14
	After	18-23	20	15-24½	21

*"Area" subtended by curves of plasma penicillin levels, with 1 hr. taken as unit of time, each 2-fold dilution of plasma representing 1 "unit" of penicillin activity, & "unit area" thus representing 1 dilution-hr. of activity. Subjects with detectable penicillin at 6 hr. assumed to have 0 level at 8 hr.

Sensitivity of Freshly Isolated Pathogens to Penicillins G and V

Preliminary comparisons were made of 55 strains of gram-positive cocci tested simultaneously on blood-agar plates containing serial dilutions of the 2 forms of penicillin. Except for staphylococci these organisms (which included pneumococci, enterococci, hemolytic streptococci and alpha-hemolytic streptococci) were either susceptible to the same concentrations of these penicillins or required twice and sometimes four times as much penicillin V as G. Of 16 strains of *Staph. aureus* 8 were slightly more sensitive to penicillin V (either completely or partially inhibited at half the minimum inhibiting concentration of penicillin G), 6 were equally sensitive, and 2 were slightly more resistant. These observations are being extended to include more strains of these and other species. Of particular interest was the fact that in these tests, done with surface cultures on blood agar containing the antibiotics, penicillin G and V were equally active on 5 recently isolated strains of hemolytic streptococci, whereas the assay strain, *Str. 98*, was significantly and regularly more susceptible to penicillin G than to penicillin V in broth containing these agents.

Discussion

It is now well recognized that relatively minor alterations in chemical structure may result in profound changes in the activity and pharmacologic properties of various drugs and hormones. Among antimicrobials this is well illustrated by the diverse sulfanilamide derivatives, which vary considerably in their activity, physical properties, absorption and excretion patterns and toxicity. Among antibiotics the early forms of penicillin that were recognized and studied — namely, penicillins F, G, K and X — showed significant differences in activity in vitro and in vivo, and some of the in vivo effects were associated with differences in their inactivation in the body.[12-14] The tetracycline analogues are more recent examples; although they are very similar in many respects, significant differences in stability, activity, absorption and distribution in the body and untoward effects in patients have been noted.[15]

Penicillin V, which differs from penicillin G by a single oxygen molecule, has been shown to have significantly different physical properties,[2-5] and is here seen also to differ in its absorption and in its activity against some susceptible bacteria. More data on blood levels have been accumulated by workers in the Antibiotics Division of the Food and Drug Administration, using different methods, but showing similarly better and more prolonged blood levels with penicillin V.[16] The relative antibacterial activity of penicillin V, as compared with that of penicillin G, varies considerably with different species and strains.[17] Preliminary clinical trials in Germany and Austria have shown penicillin V to be a practical form of oral therapy, particularly in children, and apparently effective in susceptible infections.[18-20] Its superiority over other forms of orally administered penicillin, however, has not yet been demonstrated in controlled therapeutic experiments. More data are also needed on the relative toxicity of penicillins G and V given orally.

The observations presented here indicate that penicillin V, in spite of the fact that it was less active than penicillin G, weight for weight, or unit for unit, against the test strain of streptococcus in vitro, resulted in greater and more prolonged antistreptococcal activity against the same strain in the blood after ingestion of the same amounts. This was true regardless of the relation of the doses to meals, but was particularly striking when the doses were taken after the meal. This suggests that penicillin V should be more active than penicillin G when given by mouth both in the prophylaxis and in the treatment of infections with the hemolytic streptococcus. The activity may also be greater for other infections that are susceptible to oral penicillin therapy, but this requires clinical confirmation.

The present study was carried out in only 6 subjects, but the significance of the data is markedly enhanced by the fact that all comparisons were made in the same subjects, each of whom acted as his own control. In the absence of such controls, many more subjects would be required to obtain equally significant comparisons to compensate for the considerable individual variations in absorption, such as were illustrated even in this small group of subjects.

Summary and Conclusions

A controlled study of the comparative levels of penicillin activity in the blood of the same normal subjects resulting from ingestion of single tablets of 200,000 units of penicillins G and V is reported. Penicillin V produced higher and more prolonged levels than penicillin G, as judged by the antistreptococcal and antistaphylococcal activity of the plasma; this was particularly striking when the comparisons were made with the doses that were taken after breakfast. Penicillin V produced higher and more prolonged blood levels when taken after breakfast than when taken after an overnight fast. A slowly disintegrating tablet of penicillin V was slightly superior to a rapidly disintegrating tablet of the same lot when given before breakfast, but the rapidly disintegrating tablet was superior when taken after the meal. Unbuffered potassium penicillin G yielded lower levels and less prolonged penicillemia when given after a meal than when taken fasting; however, the meal had no significant effect on the penicillin levels after ingestion of buffered penicillin G.

The numerical value assigned to the concentration of penicillin in plasma depends on the test strain used in the assay and on the type of penicillin in the standard solution employed as the control.

Preliminary observations indicated that therapeutically useful levels may be sustained during oral administration of penicillin V at intervals of four hours.

These findings suggest that penicillin V may be superior to penicillin G for oral use in the prophylaxis and treatment of susceptible infections, and further clinical trials are indicated.

References

1. Behrens, O. K., et al. Biosynthesis of penicillins. III. Preparation and evaluation of precursors for new penicillins. *J. Biol. Chem.* **175**:771-792, 1948.
2. Behrens, O. K., et al. Biosynthesis of penicillins. IV. New crystalline biosynthetic penicillins. *J. Biol. Chem.* **175**:793-809, 1948.
3. Behrens, O. K., and Kingkade, M. J. Biosynthesis of penicillins. VIII. Studies with new biosynthetic penicillins on penicillin resistance. *J. Biol. Chem.* **176**:1047-1050, 1948.
4. Brandl, E., Giovannini, M., and Margreiter, H. Untersuchungen über das säurestabile, oral wirksame Phenoxymethylpenicillin (Penicillin V). *Wien. med. Wchnschr.* **103**:602-607, 1953.
5. Brandl, E., and Margreiter, H. Acid-stable biosynthetic penicillin. *Oesterr. chem. Ztg.* **55**:12-21, 1954.
6. Giovannini, M. Vergleichende Untersuchungen von Penicillin G und Penicillin V nach oraler Verabreichung. *Wien. med. Wchnschr.* **104**:910, 1954.
7. Brunner, R. Biological testing of penicillin V (phenoxymethylpenicillin). *Scientia pharm.* **22**:151-176, 1954.
8. Finland, M., Meads, M., and Ory, E. M. Oral penicillin. *J.A.M.A.* **129**:315-320, 1945.
9. Boger, W. P., Beatty, J. O., and Flippin, H. F. Comparison of oral penicillins. *Tr. & Stud. Coll. Physicians, Philadelphia* **17**:105-114, 1949.
10. Boger, W. P., Bayne, G. M., Carfagno, S. C., and Gylfe, J. *Oral Penicillin: Evaluation of available dosage forms.* 24 pp. Norristown: Privately printed, 1953.
11. Wright, S. S., Purcell, E. M., Kass, E. H., and Finland, M. Penicillin G and benzethacil by mouth: comparison of penicillin levels in plasma of normal men after single oral doses. *J. Lab. & Clin. Med.* **42**:417-429, 1953.

12. Coghill, R. D., Osterberg, A. E., and Hazel, G. R. Relative effectiveness of pure penicillins G, X and K. *Science* **103**:709, 1946.
13. Eagle, H. Inactivation of penicillins F, G, K and X by human and rabbit serum. *J. Exper. Med.* **85**:141-161, 1947.
14. *Idem.* Varying blood levels afforded by penicillins F, G, K and X in rabbits and man. *J. Exper. Med.* **85**:163-173, 1947.
15. Welch, H., et al. Tetracycline. In *Principles and Practice of Antibiotic Therapy*. Edited by F. Martí-Ibáñez. 699 pp. New York: Blakiston, 1954. Pp. 245-261.
16. Welch, H. Personal communication.
17. Kylin, O. New bacteriological studies on phenoxymethylpenicillin (penicillin V). *Svenska lak. tidning.* **52**:464, 1955.
18. Haussman, E., and Zischinsky, H. Erfahrungen mit Ospen, einem neuartigen Oralpenicillin, im Kindesalter. *Wien. med. Wchnschr.* **103**:725-727, 1953.
19. Schindelmaisser, F. Erfahrungen eines praktischen Arztes mit "Ospen," Penicillin V, einem säurestabilen Oralpenicillin. *Wien. med. Wchnschr.* **104**:369, 1954.
20. Sinios, A. Orale Penicillinbehandlung. *Med. Klin.* **49**:2031-2033, 1954.

SALMONELLOSIS ORIGINATING IN A HOSPITAL*

A Newly Recognized Source of Infection

LAWRENCE J. KUNZ, PH.D.,† AND ORJAN T. G. OUCHTERLONY, M.D.‡

BOSTON

THE alarming occurrence of salmonellosis acquired by patients during hospitalization should always initiate an epidemiologic survey of personnel and of materials in the dietary department of the hospital. When the origin of an outbreak can be discovered, it is frequently traced to the "carrier state" of a food handler or to an improperly prepared animal food product already notorious for its implication in other outbreaks of food poisoning. Such foods include dry powdered eggs, poultry and meat products.[1]

An epidemiologic study of recent episodes of salmonellosis in patients under treatment for various disorders in this hospital has uncovered, as a source of salmonella infections, a previously unsuspected food product, dried inactive yeast (brewer's type). The results of this study are put on record principally because the recognition of contamination of dried inactive yeast by salmonellas suggests that other food products processed in a similar manner should be closely scrutinized bacteriologically. Also, this contribution to the epidemiology of salmonellosis may help reveal the origin of infection in future sporadic cases of food poisoning, the source of which usually remains unexplained.

EPIDEMIOLOGIC CONSIDERATIONS

During a three-month period salmonella infections were sustained by 5 patients in this hospital who had been hospitalized for periods ranging from six days to eight weeks before the onset of symptoms. None of the patients had symptoms of salmonellosis on admission. The diagnosis on admission in 3 cases was myasthenia gravis; 1 patient was under treatment for cancer of the colon, and the other for a cerebrovascular accident. Three of the patients were in the general hospital wards, and 2 in a private pavilion. These and other pertinent data are summarized in Table 1. The types isolated from fecal specimens of the patients were *Salmonella oranienberg* (3 patients), *S. montevideo* (1 patient) and *S. senftenberg* (1 patient).

When it was recognized that these infections had probably been contracted during hospitalization epidemiologic studies were undertaken that failed to reveal, either on the visiting or resident physician staff or among nursing personnel, a contact common to all patients. It was ascertained, however, that each of the 5 patients had been or was being fed through a stomach tube. This led the investigation to the dietary department, where again it seemed improbable that personnel were involved in the spread of infection because the tube-feeding formulas were prepared in two separate diet kitchens. An inspection of a list of the ingredients in the formulas indicated that the most promising items for bacteriologic examination were dried inactive yeast and dry milk solids. It should be emphasized that during this period the preparation of these formulas did not include boiling or heating of the ingredients or of the finished product.

TABLE 1. *Salmonella Infections Acquired during Hospitalization.*

PATIENT	AGE	SEX	DIAGNOSIS ON ADMISSION	HOSPITAL WARD OR SERVICE	INTERVAL BETWEEN ADMISSION & 1ST SYMPTOMS OF SALMONELLOSIS	SPECIES ISOLATED
	yr.					
K.R.	44	F	Cancer of colon	Surgical	8 wk.	*S. oranienberg*
P.I.	74	M	Cerebrovascular accident	Neuromedical	6 days	*S. oranienberg*
B.I.	44	F	Myasthenia gravis	Private—7th floor	9 days	*S. oranienberg*
F.L.	15	F	Myasthenia gravis	Neuromedical	6 wk.	*S. montevideo*
T.A.	18	F	Myasthenia gravis	Private—10th floor	17 days	*S. senftenberg*

*From the Department of Bacteriology, Massachusetts General Hospital, and the Department of Bacteriology and Immunology, Harvard Medical School.

†Instructor in bacteriology and immunology, Harvard Medical School; assistant bacteriologist, Massachusetts General Hospital.

‡Professor of bacteriology, University of Gothenburg, Gothenburg, Sweden; formerly, visiting bacteriologist, *pro tempore*, Massachusetts General Hospital, and lecturer in bacteriology and immunology, Harvard Medical School.

Other food materials temporarily omitted from study as unlikely sources of salmonella were pasteurized milk and cream, syrup and fresh eggs. The last, although highly suspect, were not immediately selected for bacteriologic examination because eggs for each of the two diet kitchens were purchased from separate sources. Three salmonella species were isolated from the dried inactive yeast. The spray-dried milk solids, although not sterile, were not found to contain salmonella organisms.

Bacteriologic Studies

Samples of 50 to 100 gm. of the dry powdered substance were allowed to "hydrate" for six to eight hours at 37°C. in sufficient sterile water or saline solution to form a heavy, creamlike suspension. At the end of this period aliquots of 1 or 2 cc. were transferred to tetrathionate broth tubes and allowed to incubate overnight at 37°C. These enrichment cultures were then plated on blood agar, Endo agar and SS agar. Colonies of organisms that did not ferment lactose were fished to differential tubed mediums and further identified by agglutination in commercially prepared salmonella grouping antiserums. The serologic types were identified by Dr. Ivan Saphra, of the New York Salmonella Center, Beth Israel Hospital, Department of Laboratories.

S. senftenberg and *S. montevideo* were detected among the nonlactose-fermenting enteric organisms isolated from the dried inactive yeast; the third species, *S. oranienberg,* was not recognized in earlier cultures, probably because an insufficient number of colonies were selected from the plating medium for further identification. Subsequently, when it seemed certain that more than two species were involved, the presence of all three salmonella types was recognized in the same lot of dried inactive yeast in other laboratories.

The method selected for the isolation of pathogens from the suspected foods was one that assumed only a small degree of contamination of the foodstuffs. That this was a fortunate assumption was subsequently demonstrated by the failure of conventional methods of testing to detect salmonellas in known contaminated dried inactive yeast in the bacteriology laboratory of the food manufacturer and in commercial laboratories engaged by the manufacturer for this purpose. When larger samples were tested by a procedure employing pre-enrichment "hydration" similar to the method described above, salmonellas could be isolated.

Successful bacteriologic examination of powdered foods not grossly contaminated with salmonellas seems to depend on two factors: testing of a large sample — 50 to 100 gm.; and "hydrating" of the material in water, saline solution or broth before culturing on selective or "enrichment" mediums usually employed in the isolation of pathogens from feces.

A method currently employed by food-industry laboratories for the examination of inactive dried yeast for salmonella makes use of the following mediums[2]:

Selenite broth
4 gm. of tryptone (Difco)
4 gm. of lactose
4 gm. of sodium acid selenite
4.5 gm. of potassium dihydrogen phosphate (anhydrous)
5.5 gm. of sodium phosphate (anhydrous)
1000 cc. of distilled water
1.0 cc. of 1.0 per cent L. cystine = 10 microgm. per cubic centimeter. Cystine solution is prepared by dissolving of 1.0 gm. of cystine in 15 to 20 cc. of N/NaOH and then made up to 100 cc. When ingredients are dissolved they are heated in an Arnold sterilizer for ten minutes. As an alternative method of preparation the tryptone, lactose and selenite are dissolved separately from the phosphate in 500 cc. of water each and heated in an Arnold sterilizer for ten minutes, and the hot liquids mixed together; by this method no further heating is required (cystine may be added to either portion before heating).
Tetrathionate broth (Kauffman's modification).
46 gm. of Difco tetrathionate base.
1000 cc. of water.
40 gm. of calcium carbonate (precipitated chalk) and 20 gm. of sodium thiosulfate.
Autoclave for twenty minutes under 15 pounds' pressure.
Iodine solution:
20 gm. of iodine
25 gm. of potassium iodide
100 cc. of distilled water.

At first only a small portion of water is added, and the mixture is shaken. Iodine dissolves more rapidly in concentrated potassium iodide. When the iodine is dissolved the remainder of the water is added.
Brilliant-green solution, 0.1 per cent.
Just before use, to each 100 cc. of tetrathionate broth, 1 cc. of the 0.1 per cent brilliant-green solution and 2.0 cc. of iodine are added, and the solution is thoroughly mixed.

Method

To 50.0 gm. of inactive yeast 200 cc. of sterile distilled water is added, and the mixture is thoroughly shaken and incubated overnight at 30°C. (It is best to start the sample the first thing in the morning, to give full twenty-four hours of pre-enrichment.)

From the well mixed pre-enriched material, 1 cc. is transferred to 10 cc. each of selenite and tetrathionate broth.

After five or six hours the selenite cultures are

streaked on brilliant-green agar plates (Difco) and SS agar plates (Difco).

After twenty-four hours both selenite and tetrathionate cultures are streaked on SS agar plates. The tetrathionate-inoculated tubes are held for forty-eight hours after which cultures that were negative in twenty-four hours are streaked.* It is not necessary to hold selenite cultures longer than twenty-four hours. Confirmation of the presence of salmonella is made by direct agglutination tests in group antiserums A, B, C_1, C_2, D and E, material picked from suspected colonies being used as an antigen. Suspected colonies are also inoculated into Kligler's or triple-sugar-iron (TSI) agar slants for further study.

Discussion

It is, of course, pertinent to the present problem that salmonella infections after the ingestion of contaminated dried inactive yeast occurred in a hospital, where epidemiologic studies are easily pursued. However, emphasis should be diverted from dried inactive yeast per se, the processing of which does not peculiarly involve or promote contamination with salmonella. Rather, consideration should be given to the fact that this is one of many dried food products, all of which may be subject to the same hazards of contamination by potentially pathogenic agents, as indicated below.

In the present study all shipments of the particular lot of dried inactive yeast were recalled by the manufacturer, who immediately undertook an investigation of the processing plant to determine the source of the contamination. Salmonellas were not detected in either equipment or yeast from the culture tanks, separators, holding tanks, drying drums or intermediate conveyors.

It was only during the final stages of milling, screening and packaging that salmonella organisms were occasionally found in samples of the almost finished product. The sporadic nature of the contamination and the elimination of other possible sources of the pathogenic bacteria led to the discovery that these micro-organisms were being introduced from the air outside the building through a ventilating duct. No obvious source of the air contamination has been discovered. Since the introduction of air filters in the ventilating system, further contamination with salmonellas has not been recognized.

Salmonellas are widely distributed among animals and are frequently found in animal excreta. It is not difficult to appreciate that air may at times contain small numbers of these bacteria; that they are insufficient in numbers to initiate infections by the respiratory route may account for the fact that their presence in air has escaped much attention thus far.

It may further be assumed that the degree of contamination in the finally packaged product is not sufficient to initiate salmonella infections by the oral route but rather that additional conditions of incubation under appropriate circumstances of time, temperature and humidity are necessary to permit the multiplication of the pathogenic bacteria to numbers sufficient to cause disease when the final foodstuff is ingested. Also to be considered is the probability that susceptibility to infection by small numbers of salmonellas depends on the age and physical condition of those exposed.

Finally, attention might be called to sporadic cases of salmonellosis, the origin of which is infrequently recognized. It might be interesting to consider whether other more widely distributed processed foods are associated with such occurrences. If incubation to permit growth of pathogens to infectious levels is required before a contaminated food becomes a hazard to health, refrigeration of these foods in liquid form is an absolute necessity. However, more important are the assurances of the manufacturers of the product involved in this study that conditions permitting contamination of the food have been recognized and eliminated, and that the more adequate methods of detecting small numbers of enteric pathogens have been introduced into their routine of testing for the presence of such bacteria. It is not unreasonable to assume that similar studies and precautions are being adopted by other representatives of the food industry.

Summary

The occurrence of salmonellosis in 5 hospitalized patients is described from the epidemiologic and bacteriologic points of view. Investigation revealed that all the patients had received tube-feeding formulas that included dried inactive yeast contaminated with three species of salmonella at the processing plant. Theoretical and practical implications are discussed.

References

1. Weil, A. J., and Saphra, I. *Salmonellae and Shigellae: Laboratory diagnosis correlated with clinical manifestations and epidemiology.* 252 pp. Springfield, Illinois: Thomas, 1953. P. 178 ff.
2. North, W. R. Personal communication.

*If other appropriate procedures for isolation and identification of salmonellas are preferred they may be substituted in the method at this point.

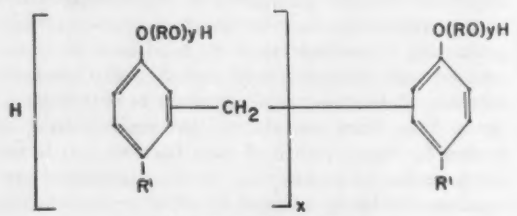
ALEVAIRE AS A MUCOLYTIC AGENT

MAURICE L. TAINTER, M.D.,* FREDERICK C. NACHOD, PH.D.,† AND JOSEPH G. BIRD, M.D.‡

RENSSELAER, NEW YORK

THE use of detergents in the liquefaction of thick mucoid and purulent exudates in the alveoli and bronchial tree was not practical until recent years, owing to the fact that no surfactant with appropriate properties was known. Agents that lower surface tension had long been used in suppurating wounds and body cavities. Their value in cleansing and in aiding the penetration of infected tissues by chemotherapeutic agents is well established. The application of this action to infections and other conditions of the lower respiratory tract has now become quite extensive through the use of the new detergent superinone in a balanced formulation (Alevaire§).

Superinone, a nonionic surface-active agent, formerly identified as Triton A-20 and Triton WR-1339, is unique in that it is practically nonirritating and nontoxic[1,2] and does not hemolyze red blood cells in a thousand times the concentrations at which other detergents are hemolytic.[1] Marked lowering of surface tension is provided by the 0.125 per cent concentration present in Alevaire. It is an alkylaryl polyether alcohol polymer with the following chemical formula:



STRUCTURE OF SUPERINONE

Superinone. R=ethylene; R^1=tertiary octyl; x is > 1 but <6; y=8 to 10.

Further mucolytic action is provided by 2 per cent sodium bicarbonate. Cleavage of large molecules into smaller ones is caused by a rise in the pH of many proteins, with resultant decrease in viscosity. A pH of 8.3 is attainable in such solutions without irritation through the use of the sodium bicarbonate. Five per cent glycerin is also present in Alevaire, to prevent evaporation of droplets, to stabilize droplet size and to assure the carrying of actual liquid droplets into the bronchial passages.

Superinone was administered by aerosol to tuberculous patients by Miller[2] and to infants and children by Miller and Boyer,[3] beginning in 1949. Their report on approximately 300 cases[3] established its safety and efficacy as a detergent in the presence of viscid bronchopulmonary secretions. This has been confirmed, often with dramatic results, in extensive use in both children and adults.[4-7] More than a hundred articles have reported on the use of Alevaire aerosol therapy in a number of respiratory-tract conditions, including bronchitis, bronchiectasis, asthma, atelectasis, pneumonia, tuberculosis, neoplastic disease, atelectasis and hyaline-membrane disease of the newborn, and a number of other processes in which sputum or viscid secretions are produced. The agent has also been used prophylactically in certain of these as well as in postoperative atelectasis and pneumonia. It is particularly indicated in tracheotomized patients. It has been shown experimentally in guinea pigs that Alevaire effectively protects against the formation of hyaline membranes produced by exposure to 98 per cent oxygen.[8]

Other agents, such as antibiotics, bronchodilators, bronchovasoconstrictors, antihistaminics and proteolytic enzymes, may be dissolved in Alevaire for combined therapy. The types of apparatus that give the critical droplet size, 0.5 to 3.0 microns, and other technical aspects of clinic and home use of aerosols have been described.[4,9-11]

The reports of the beneficial effects from its detergent action on the alveolar and bronchial membranes and viscid tenacious sputum have been based mainly on clinical observations. The reduction of infant mortality, the profound improvement of patients and the obviously thinner consistence of the sputum, with increased expectoration, have comprised the evidence of the value of this therapy. This is logical, for such experience is the final proof of efficacy.

However, the physical chemistry involved in the interaction of Alevaire and bronchial secretion or exudates has not been adequately explored. Ravenel[4] studied the viscosity of bronchiectatic sputum, saliva and amniotic fluid. Alevaire mist, bubbled through these materials, lowered their viscosity by 19, 10 and 24 per cent, respectively.

Clinical observations of the character of sputum before and after Alevaire therapy have repeatedly shown that viscous, sticky masses are converted to thinner, more voluminous material that is more readily expectorated. Apparently, the viscosity is lowered by the dilution of the thick sputum by the water present in Alevaire and also perhaps by thinner bronchial secretions induced by its ingredients. We have shown in vitro that the addition of Alevaire to sputum does lower the viscosity as measured in an Ostwald viscosimeter, thus confirming Ravenel's findings. The water-depositing action of Alevaire aerosol inhalation is an important element in the lowered vis-

*Director, Sterling-Winthrop Research Institute.

†Head, Physical Chemistry Section, Sterling-Winthrop Research Institute.

‡Clinical pharmacologist, Sterling-Winthrop Research Institute.

§Available from Winthrop-Stearns, Incorporated, New York City.

cosity reported by clinicians, but may not completely explain the observed changes.

Macklin[12] developed a concept of the dimensions of the pulmonary alveolar mucoid film that is reproduced in Figure 1. This suggested that an important action of a mucolytic agent might be to lower the interfacial energy. The arrow indicates the probable site of attack of the surfactant according to this concept. This proposes a reasonable mechanism for the "rolling up" of the layer of mucus. It is supported by various investigators,[7,13,14] who have pointed out that local deposition of wetting agents will reduce surface tension in the interface between mucous membranes in contact, thus eliminating cohesion of moist surfaces, which is the main factor resisting aeration of atelectatic lung tissue. Similarly, in mucus-obstructive diseases, wetting agents loosen retained mucus secretions from the mucous membranes by their emulsifying action. By continuous deposition on the surface of these secretions the detergent assists in their elimination and the restoration of normal drainage.

To test this hypothesis we have carried out in vitro experiments to measure surface-tension effects. The surface-tension lowering of the sputum by the surfactant superinone was demonstrated with a duNoüy tensiometer, and is shown graphically in Figure 2. The surface tension of water at 25°C. is 72 dynes, and that of Alevaire 37.5 dynes per centimeter. The surface tension of homogenized sputum remained approximately 52 dynes per centimeter, without change,

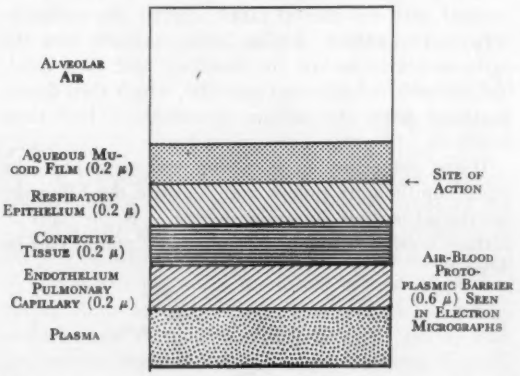

Alveolar Air
Aqueous Mucoid Film (0.2 μ)
Respiratory Epithelium (0.2 μ)
Connective Tissue (0.2 μ)
Endothelium Pulmonary Capillary (0.2 μ)
Plasma
← Site of Action
Air-Blood Protoplasmic Barrier (0.6 μ) Seen in Electron Micrographs

FIGURE 1. *Dimensions of the Pulmonary Alveolar Mucoid Film and Site of Action of Alevaire (Based on Macklin[12]).*

as water was added. However, addition of Alevaire reduced the surface tension of the sputum approximately 20 per cent, as shown by the lower curve in Figure 2.

The gluelike tenacity of sputum and mucus that have lost water through evaporation is a matter of common observation. Dehydration of secretions in the bronchial tree by respiratory air flow is increased by breathing, especially when tachypnea is present as an effect of the pathologic state. These thickened secretions are capable of sticking tenaciously to the bronchial or alveolar walls. Coughing, even when quite forceful, is frequently ineffective in clearing such material from its attachment to the pulmonary membranes.

Ciliary action is at optimal efficacy only when there is a layer of sufficiently thin fluid covering the surface. Otherwise, the cohesive force of the thickened mucoid system retards the ciliary motion. Patients of this

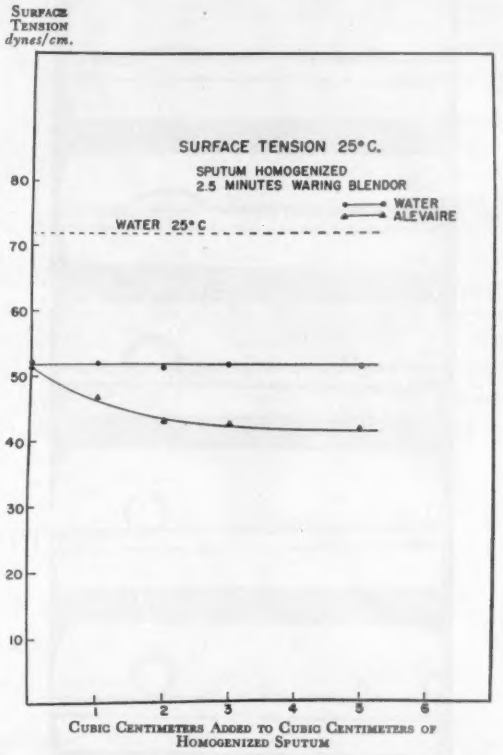


FIGURE 2. *Effect of Alevaire on Surface Tension of Sputum.*

type usually must wait until this sluggish ciliary action transports the sputum mass to the trachea or large bronchi before they can dislodge it by coughing, if at all. The role of pastelike aggregations of sputum in plugging bronchial subdivisions and in the production of atelectasis, bronchopneumonia and bronchiectasis was long ago described by pathologists. The danger of extension of these and other conditions into the parenchyma of the lungs is increased as long as there is sputum that adheres tenaciously to membranes. The dislodging of large plugs, believed to have been present in bronchi for months or years, has been reported after prolonged use of Alevaire therapy.

We have attempted to determine if such adherence to a surface can be shown in the laboratory, and if any diminution of it by a surface-tension-lowering agent can be demonstrated. For this purpose we have used ground-glass plates as models for the bronchial or tracheal surfaces. When such a plate is wet with

water and inclined at various angles, a measured quantity of sputum can be dropped upon the wet surface and its descent by gravitation timed. We have found a 45° angle to be the most practical. Moderate mixing of the sputum beforehand is desirable in the tests, to provide homogeneity in successive samples from any given lot of sputum. This allowed the use of drops of sputum of comparable size and consistence whose behavior was consistent.

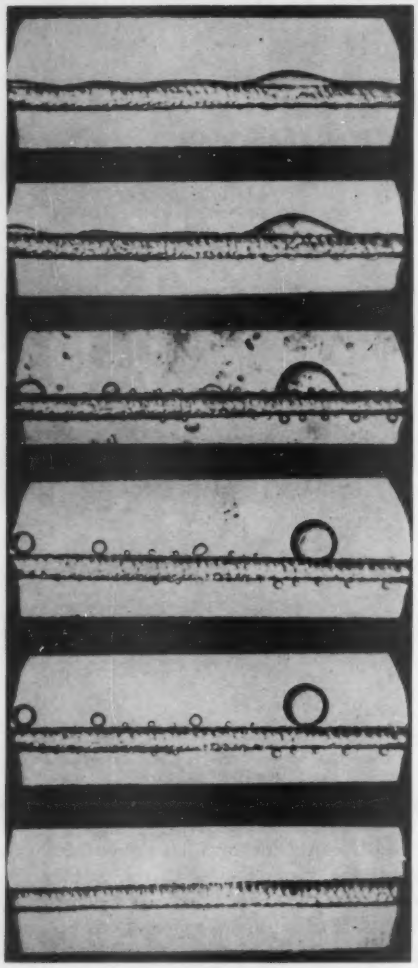


FIGURE 3. *"Rolling-up" Mechanism Described by Palmer[15] and by Adam and Stevenson.[16]*

The average time required for the sliding of a measured volume of sputum a distance of 15 cm. on the water-wetted ground-glass surface was four and six-tenths seconds. However, the sputum often adhered to the glass and stopped its descent completely. When the glass was immersed in Alevaire the time was only one and a half seconds for an aliquot of the same sample of sputum. The striking difference was repeatedly confirmed with different lots of sputum.

These results demonstrated that the adhesive attraction between the sputum mass and the wet surface is greatly reduced by the lowering of surface tension in the thin Alevaire film that covers the glass. The surfactant pre-empts the surface of the large drop of sputum as it slides down the plate. A type of lubricating action is thus provided by the detergent properties of Alevaire. Such a physical effect is undoubtedly present in the bronchial tree in the clinical use of this agent.

Alevaire inhalation, with proper technic, allows the minute droplets of water, surfactant, glycerine and bicarbonate to collect on all the respiratory membranes, probably including the alveolar walls.[8] The droplets can spread out and cover the ciliated and respiratory membranes with a very thin fluid. Adhering mucus is likewise covered by the Alevaire, and its surface is easily permeated by the surfactant. Deeper permeation is conceivably caused by movement of the sputum in the bronchi under the influence of respiratory motion and air flow. To-and-fro movements would help the mixing of Alevaire and sputum, and expose more mucous-membrane surface to coverage with the Alevaire constituents.

A sequence of microphotographs have been published that depict a comparable "rolling up" of a viscous substance by the effects of a surface-active agent. The system reported by Palmer[15] and by Adam and Stevenson[16,17] consisted of wool fibers greased with red-stained lanolin under the action of cetyl sodium sulfate. Figure 3 shows clearly how the surfactant attacks first the interface and then gradually loosens the adherent material, which then finally separates from the surface to which it had been attached.

If the subscripts e, m, a are used to denote the phases epithelium, mucus and Alevaire the following interfacial-tension equation, where γ is the unit of surface tension in dyne per cubic centimeter, can be devised:

$$\gamma_{e,m} = \gamma_{e,a} + \gamma_{a,m} \cos \vartheta_{a,m}$$

or

$$\cos \vartheta_{a,m} = \frac{\gamma_{e,m} - \gamma_{e,a}}{\gamma_{a,m}}$$

Alevaire deposition will tend to decrease $\gamma e,a$ and $\gamma a,m$ and hence increase the contact angle $\theta a,m$, which will bring about the separation of mucus from the bronchioles and other sites.

We believe that these mechanisms, as demonstrated in selected model in vitro experiments, help to explain and illustrate the beneficial action of Alevaire in the treatment of most congestive conditions of the lungs.

Summary and Conclusions

The rationale for the application of a detergent material to exudative tracheobronchial and pulmonary diseases is discussed.

The surface tension of partially homogenized sputum is markedly lowered by the addition of Alevaire, but not by that of water.

The physicochemical forces involved in the mucolytic action of Alevaire are related to the lowering of interfacial tension as demonstrated by direct surface-tension measurements. The pre-emption by the surfactant of the mucus-epithelium interface brings about a change in contact angle, thus permitting the "rolling up" and separation of the mucus from the mucosa. When this has been accomplished expulsion of the mucus is facilitated.

The water-saturated atmosphere inhaled in the proper use of Alevaire arrests the dehydration of sputum in the lungs and of the respiratory membranes. The admixture of this agent with viscid sputum also dilutes the sputum, thereby lowering its viscosity *in situ*, further facilitating its expectoration.

Alevaire, as an aerosol, may be considered a true topically acting expectorant. It may also serve as a deeply penetrating surface-active vehicle for many drugs, including bronchodilators and antibiotics.

The experimental assistance of Mr. M. Priznar is gratefully acknowledged. Sputum for these studies was supplied through the kindness of Drs. Edmund G. Beacham and Vernon H. Langeluttig, Baltimore City Hospitals, and of Dr. George Marthy, Albany Hospital, New York.

References

1. Glassman, H. N. Hemolytic activity of some nonionic surface-active agents. *Science* **111**:688, 1950.
2. Miller, J. B. Applicability of surface-active agents in aerosol streptomycin therapy of pulmonary tuberculosis. *Quart. Bull., Sea View Hosp.* **10**:155-160, 1948.
3. Miller, J. B., and Boyer, E. H. Nontoxic detergent for aerosol use in dissolving viscid bronchopulmonary secretions. *J. Pediat.* **40**:767-771, 1952.
4. Ravenel, S. F. New technique of humidification in pediatrics. *J.A.M.A.* **151**:707-711, 1953.
5. Miller, J. B., et al. Alevaire inhalation for eliminating secretions in asthma, sinusitis, bronchitis and bronchiectasis of adults: preliminary report. *Ann. Allergy* **12**:611-626, 1954.
6. Sadove, M. S., Miller, C. E., and Shima, A. T. Postoperative aerosol therapy. *J.A.M.A.* **156**:759-763, 1954.
7. Farber, S., and Wilson, J. L. Atelectasis of new-born: study and critical review. *Am. J. Dis. Child.* **46**:572-589, 1933.
8. Bruns, P. D., and Shields, L. V. High oxygen and hyaline-like membranes. *Am. J. Obst. & Gynec.* **67**:1224-1236, 1954.
9. Kracum, V. D., and Collins, V. J. Aerosol administration of Alevaire. I. Technics. *New York State J. Med.* **54**:2083-2086, 1954.
10. Ravenel, S. F. Respiratory infections in infants and children. *GP* **10**:40-48, 1954.
11. Vigneck, A. J., and Nicholson, R. L. Autonomous premature unit. *Pediat. Clin. North America* **1**:661, 1954.
12. Macklin, C. C. Pulmonary alveolar mucoid film and pneumonocytes. *Lancet* **1**:1099-1104, 1954.
13. Gruenwald, P. Surface tension as factor in resistance of neonatal lungs to aeration. *Am. J. Obst. & Gynec.* **53**:996-1007, 1947.
14. Denton, R. Continuous nebulization therapy. *Pediat. Clin. North America* **1**:625, 1954.
15. Palmer, R. C. Effect of salts on detergence. *(Tr.) Soc. Chem. Ind., London* **60**:56-60, 1941.
16. Adam, N. K., and Stevenson, D. G. Detergent action. *Endeavour* **12**:25-32, 1953.
17. Adam, N. K. Detergent action and its relation to wetting and emulsification. *J. Soc. Dyers & Colourists* **53**:121-129, 1937.

SPECIAL ARTICLE

SCHOOL HEALTH AND THE FAMILY PHYSICIAN*

Kenneth L. Maclachlan, M.D.†

MELROSE, MASSACHUSETTS

THE purpose of this paper is to encourage family physicians to understand better the aims of the school-health program, to emphasize the necessity of keeping school children under the family instead of the school physician, to foster individual private rather than collective state examination for school children and to make family physicians realize that the proper examination of school children according to the school-health regulations allows the private practice of medicine to reach the children during their formative years, thus encouraging the implantation of the idea of private in contradistinction to socialized medicine. It might even be pointed out that there is a certain financial return to the family physician who conscientiously carries out the school-health examination among his private patients. For purposes of clarity family physician is synonymous with personal physician, private physician or physician in private practice as distinguished from school physician, school medical advisor, school-health officer, health-department physician and so forth. The problems of state aid, differences in rural and urban areas, over-all school-health education programs, complete health-appraisal procedures, mental-health programs, school-athletics programs and methods of intercommunication between the schools and the private physician are fully realized but are not the particular concern of this paper. However, it is paramount for the family physician to accept the fact that, except under a complete or semicomplete system of socialized medicine, the state health department or even a local medical-society committee can never relieve him of the responsibility of active participation in the school-health program.

On July 9, 1951, an act was passed by the Commonwealth of Massachusetts regulating physical examinations of school children in which it was stated that every child in the public schools shall be separately and carefully examined at intervals to be determined and that tests of sight and hearing

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 19, 1955.

†Chief of obstetrics, Melrose Hospital.

shall be performed in accordance with regulations set up by the Department of Public Health. The Department of Public Health has made certain regulations effective September 1, 1952. The preamble to these regulations states, in part, as follows:

> That the health appraisal should be done by the family's own physician whenever possible and the results recorded on forms approved by the Department of Public Health. Also at the same time, the physician should be furnished with a copy of the screening tests performed in the school. The examination shall be done within six months before entrance to school or during the first year after entrance and at intervals of either three or four years thereafter. The vision and hearing is to be tested in the first grade and annually thereafter. The health appraisal shall be done with such care and detail as to command medical respect and be a desirable educational experience for the child. Rectal and vaginal examinations shall not be done by the *school* physician. Disabilities and defects shall be brought to the attention of the family and the latter shall be encouraged to take the child to the family physician. The above are minimum regulations only.

Joint committees on child health and school health of the American Public Health Association and the American Academy of Pediatrics have prepared statements of the basic principles that should govern health programs for children of school age, including the following recommendations, which have been endorsed by the Massachusetts Medical Society:

> In a program for child health there should be the maximum continuity of health supervision. The ideal for quality and to a great extent for *economy* would be continuous supervision and one continuous record from infancy through childhood as is often provided by the child's own physician whenever possible. The school health appraisal should not include diagnosis and treatment. Adequate utilization of the child's own physician should give continuity in *health* and *illness, combine* responsibility for diagnosis and treatment, and *centralize* responsibility for the health problems of the entire family. The physician should send a report of his findings *and* recommendations for the guidance of school personnel. The periodic examination within the school applies to all children who do *not* go to their own physician.

The Committee on School Health of the Massachusetts Medical Society is entrusted with the duty of meeting the health needs of school children in accordance with State and federal regulations and recommendations. The Committee attempts to maintain liaison with the societies of otolaryngology and ophthalmology for guidance in their particular fields. The Committee confers with the Massachusetts Department of Public Health in an attempt to provide the necessary medical care and to guard against further encroachment on the private practice of medicine. The Committee is sponsoring this paper in the hope that the private family physician will realize that it is his duty, his responsibility and his opportunity to enter the program of school-health examination and appraisal in a manner to command medical respect so that the private practice of medicine will be the child's — and the parents' — first choice in school as well as elsewhere.

It might be well to review briefly the forms at present recommended by the Department of Public Health.

The form sent to the parent is as follows:

> Dear Parent:
>
> _____ is scheduled to have a school health examination this year. Because your family physician has a comprehensive knowledge of the health status of your child, you may desire to have him perform this examination. If so, please let us know before _____ and we will send you a school record form upon which your child's physician may record his findings at the time of the examination.
>
> If we do not hear from you by this date we will make arrangements to have this examination done by the school physician.
>
> Sincerely yours,
>
> _____

Most schools do, and all schools should, notify the parents that the school-health examination is to be done during a certain period and that the examination may be done by the family's own physician. If the parents elect to have the examination done by their own physician, this notice, which is on the reverse side of the school-health examination record, is sent to the physician. The actual report and examination are no more than are consistent with any conscientious examination given by a physician to any child; the form sent to the doctor is as follows:

> Date _____
>
> Dear Doctor:
>
> The parents of _____ (name) _____ (address) have requested that the school health examination required by law be done by you. Please fill out the form on the reverse side of this sheet and include in the paragraph entitled "Remarks" anything concerning this child's state of health, physical and mental growth and development, nutrition, and so forth that would be of value to us in helping him to secure the greatest possible advantage from his educational opportunity.
>
> The information supplied by you will be available only to the personnel of the school health services and will be regarded as confidential.
>
> Sincerely yours,
>
> _____

For purposes of clarity it should be understood that the "school-health examination" is that phase of the health appraisal which is conducted by physicians and dentists. The record of the examination is as follows:

> MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH — MASSACHUSETTS DEPARTMENT OF EDUCATION
>
> Family Physician's Report on School Health Examination
>
> NAME OF PUPIL _____
>
> PREVIOUS DISEASES AND OPERATIONS
>
> RECORD OF IMMUNIZATION
>
> PHYSICAL EXAMINATION
>
> Height _____
>
> Weight _____
>
> Nutrition _____
>
> General body type _____
>
> Posture (remark on presence or absence of scoliosis and lordosis, and define scoliosis as functional or organic)
>
> Skin _____
>
> Eyes _____
>
> Ears _____

Nose ———
Mouth ———
Teeth ———
Pharynx ———
Thyroid ———
Lymph glands ———
Breasts ———
Lungs ———
Heart ———
Blood pressure ———
Pulse rate at rest ——— After exercise ———
2 minutes after exercise ———
Abdomen ———
Hernia ———
Pilonidal sinus ———
Genitalia ———
Skeleton ———
Feet ———
Reflexes ———

LABORATORY TESTS

Date	Test	Result
———	Tuberculin	———
———	Chest X-ray	———
———	Hemoglobin	———

Urinalysis ——— Date ———
Specific gravity ——— Result ———
Albumin ——— Result ———
Sugar ——— Result ———
Microscopic ——— Result ———

Is this child capable of carrying a full program of school work including gymnastics and athletics? Yes— No—
Must the school program be modified to meet the needs of this child? Yes— No—
By restriction of use of stairs? Yes— No—
By special seating accommodations? Yes— No—
Other (specify) ———
Does the pupil have any irremediable defects? Yes— No—
REMARKS:
Date ——— Signature of Physician ———

If the family physician has completed at a previous school-health examination the "previous diseases and operations" and also "record of immunization" a simple notation of "previously reported" is sufficient since these reports are carried by the school system as a cumulative record. If there is additional information it should be recorded. On the actual physical examination the importance is not to quibble concerning the actual choice of words but to present the physical picture of the child. Under nutrition the words "excellent," "normal" and "average" may all be used, as well as "emaciated," "marasmic" and "undernourished," without necessitating a check list. The general body type can be average, tall and slender, short and fat or, if indicated, cretinistic and so forth. Because of the importance of functional as well as organic postural changes several hints are given. Under skin the presence of eczema or of dermatitis in its various forms should be noted. The actual visual test is done in the schools, but presence of conjunctivitis, congenital blindness, old operative scars, blepharitis, squint and so on should be mentioned. The ears should be examined by otoscope, and cerumen removed, and notation of perforated tympani and other abnormalities made, the hearing being left for school audiometer test unless the examiner has the necessary apparatus. And so on as indicated under the various headings of the examination. The newer forms request blood pressure and pulse only as indicated. The laboratory tests are only "as indicated," but this is where the family physician really becomes the important factor. Laboratory tests are *not* done in the schools. Magazines, newspapers, radios, televisions and medical literature are literally bombarding the population with the dangers of unrecognized tuberculosis and the false security of free x-ray examinations, of tiredness and lack of energy from tired blood, of latent diabetes, of various preventive inoculations, of the danger of removing tonsils and adenoids, and so forth — many of which are accepted by the population at face value. The family physician rebels at having to fill out another form at the price of an office visit, but he is here given an opportunity, under a system required by law, to practice preventive medicine and to educate the youth of today, who will be the parents of tomorrow, in proper medical care as opposed to advertising and lay medical care. How can an intelligent physician fail to take full advantage of such a situation?

The rest of the report deals with the physician's opinion of school activities. And not to be taken lightly is the space for "Remarks." If there is some emotional problem at home or an adjustment problem inherent in the child, if slow adolescence is apparent, if undue exuberance or extreme shyness is noted, or if there is anything that might aid either the school or the parent such items should be briefly mentioned here.

As far as I can determine the family physician performs the vast majority of the preschool examinations, except in the large industrial cities, less than a third of the examinations for those in the third and fourth grades, a smattering of those in the seventh and eighth grades and practically none of those in the eleventh and twelfth. Has the family physician failed to educate the child and the parent properly in matters of health, or are there other more important reasons?

Conclusions

The family physician must assume a more active part in school health and primarily in the school-health examination since it is through him that: definitive treatment of defects can be carried out, laboratory tests can be performed, closer contact with the entire family as well as the child can be fostered, the proper balance between private medical enterprise and collective state regulations can be maintained, the intimate relation between the child, his family and the family physician can be strengthened and the progressive experience of medical education and proper health attitudes can be instilled into the lives of school children.

MEDICAL PROGRESS

TREATMENT OF MIGRAINE (Continued)

JOHN R. GRAHAM, M.D.*

BOSTON

THERAPY OF THE ACUTE ATTACK

General Principles

Wolff[16] has suggested that the migraine experience serves a biologic need. The pain and generalized distress of the attack force the patient into the retirement from the stressful life scene that his exhausted physique is demanding. It is well to bear this in mind, both in providing the setting for the treatment of the acute attack and in governing the speed with which the patient returns to activity if drug therapy is successful in relieving the pain. The patient needs to learn that, thankful as he may be that his head pain is gone, he should still respect its significance and alter the day's activities in such a way that rest is achieved. Otherwise, there is a tendency for the next attack to appear more quickly. A period of rest, a quiet, dark room, freedom from oversolicitous relatives and, frequently, mild sedation form the background of all treatment of acute attacks. Occasionally, removal to a hospital is necessary in very stubborn attacks. There, a complete divorce from responsibilities and a tense home atmosphere may be achieved, and analgesic and sedative medication, replacement of electrolytes and other services may be provided, with dramatic relief to an otherwise seemingly interminable and intolerable situation.

Having taken pains to obtain the proper setting for treatment of the attack, the physician turns next to the selection of the proper drugs to bring relief. In mild cases the administration of salicylates, combinations of salicylates with caffeine and mild sedatives of the barbiturate group may be sufficient. When these fail, in certain situations in which more specific drugs (to be mentioned) cannot be tolerated and the headaches are not so frequent that addiction may become a problem, the use of codeine, Demerol and opiates may be justified. Injectable narcotics, however, should never be placed in the hands of the patient or of a relative or spouse. Relatives and husbands are usually so involved emotionally in both the precipitation and the treatment of the attacks that they make poor doctors. This is particularly true of the migrainous wife of a physician. Such a patient should be made to seek treatment from another physician, as any other patient does; otherwise, disastrous addiction and a very unhappy domestic situation may develop.

*Chief, Medical Service, Faulkner Hospital; clinical associate in medicine, Massachusetts General Hospital.

Ergot Preparations

When a patient has migraine so severely that he is willing to undergo the trouble and expense of seeking help from a physician, he has usually tried all the ordinary sedatives and analgesics and found them inadequate. Consequently, the discovery that ergot derivatives can terminate severe attacks in a high percentage of cases has been the most important single contribution to the therapy of this disease.

History of the introduction of ergot alkaloids into the therapy of migraine. Since ergot has proved to be such a useful weapon in migraine and since the history of its use in this regard does not seem to have been recorded systematically in any one publication, it seems worth while to present a short account of the facts as they may be gleaned directly and indirectly from the available literature.

In 1883 Eulenburg[17] reported on the effectiveness of injections of "Ergotinum citricum solutum" for "vasomotorische Cephalalgie" and "vasoparalytische Form der Hemikranie."

In 1894 a summary of a paper read by W. H. Thompson[18] reported that he had found "tincture of ergot" useful both by mouth and by rectum in the treatment of a "number of cases of severe periodic neuralgias," and at this meeting Joseph B. Collins described a woman with menstrual migraine who discovered accidentally a cure for her migraine headaches when she took tincture of ergot for her menorrhagia.

The next landmark was the isolation by Stoll,[19] in 1918, of ergotamine tartrate and the demonstration of its sympatholytic powers. With this discovery ergotamine began to be used in the treatment of a number of conditions that were considered to be due to overactivity of the sympathetic nervous system.

In 1926 Maier,[20] using ergotamine as an "inhibiteur du sympathique," described the effectiveness of this medication in migraine, epilepsy, thyrotoxicosis, urticaria and "postoperative tetany."[20]

Two years later Tzanck[21a] reported before the Société Médicale d'Hôpitaux de Paris on the effectiveness of ergot in stopping the migraine attack, and referred to the fact that it had recently been similarly used by Declayrfat, Cornil, Étienne and Caussade[21b] and Netter. At the same meeting Flandin discussed its successful use in a case of menstrual migraine.

In the same year Trautmann[22] wrote a similar report, and in 1928 and 1929, Shedrow, Targhetta, and Cantilo are said to have recorded the same (reports not available to me).

In 1932 the first paper in the English literature (except for the early accounts by Thompson and Collins referred to above) appeared in the *Medical Journal and Record*, in which Ignelzi[23] described the dramatic relief received by 6 migraine sufferers from an injection of 0.5 cc. of ergotamine tartrate.

In 1934 three groups of workers in the United States reported on the effectiveness and specificity of this therapy: Lennox,[24] in Boston, Brock, O'Sullivan and Young,[25] in New York City, and Logan and Allen,[26] at the Mayo Clinic. Since that time a wealth of literature has developed confirming these original observations, exploring the mechanism by which ergot derivatives achieve their result and dealing with the matters of dosage, route and principles of administration, side effects, toxicity and drugs that are useful as adjuvants or serve to counteract the unpleasant effects of ergot itself. It is beyond the scope of this report to review them all in detail, but it seems worth while to register herewith the main concepts that have arisen regarding ergot therapy.

Mechanism of action of ergot derivatives. The original use of ergotamine tartrate for migraine was based on the fact that migraine was considered by many to result from an overactivity of the sympathetic nervous system, causing cerebral vasoconstriction, and ergotamine was known to be sympatholytic. That this is not its important action in the relief of headache has become apparent in more recent years by dint of observations that in the human subject suffering from the painful phase of migraine, vasodilatation is present rather than vasoconstriction; that, at the height of relief achieved by ergotamine, there is evidence that sympathetic responses are intact, as demonstrated by skin-temperature observations in the region of headache[11] and measurements of the electric resistance of the skin[27]; and that ergotamine has a constrictive effect on blood vessels in a sympathectomized limb.[28] The development of newer derivatives of ergot that have less direct constrictive effect on the smooth-muscle coats of arteries and much more sympatholytic effect than ergotamine tartrate has helped to settle this matter. These drugs are effective in stopping migraine headache directly in proportion to their capacity to contract arteries and in inverse proportion to their sympatholytic powers.[29]

Pool and Nason[30] demonstrated that in the cat the injection of ergotamine caused constriction of the dural arteries. The studies of Wolff and his coworkers[11] have shown that relief of migraine from ergotamine is always associated with decrease in pulsation and constriction of cranial arteries, especially the branches of the external carotid artery. Since it is known that ergotamine has a direct effect on the smooth muscle of arteries and since it has been shown that headache relief is associated with such constriction and not with demonstrable inhibition of sympathetic impulses or with any analgesic action,[31] it seems logical to assume that the main beneficial influence of ergotamine in headache is derived from its capacity to constrict the smooth muscle of arterial walls. Bluntschli and Goetz,[28] in interesting human plethysmograph experiments, have demonstrated that ergotamine tartrate used in clinical doses in man not only has a direct constrictive effect on arterial walls but also has a depressant effect on vasomotor centers high in the central nervous system. It is possible that this last phenomenon has some part, probably a distinctly minor one, in the effectiveness of ergotamine in stopping the pain of migraine.

Preparations of ergot derivatives now on the market that are useful in migraine. The various forms in which ergot derivatives are now available, some of their properties and the routes by which they may be administered are listed below. Table 1 summarizes a suggested schedule of dosage. Ergot should be given as soon as possible in the attack. The initial dose may need supplemental increments at intervals of half an hour to one hour until relief is obtained, toxicity develops or the maximum dose has been given. When the total effective dose has been determined, a large proportion of this should be given in subsequent attacks at the onset.

Ergotamine tartrate pills (Gynergen): 1 mg. for oral use, either sublingually or for ingestion. This is the least effective and most unreliable form of ergot therapy. To obtain headache relief, more ergot is required by this method, and more unpleasant side effects are created.

Ergotamine tartrate, 1 mg., combined with caffeine alkaloid, 100 mg. (Cafergot): an effective oral medication, but still fraught with side effects, occasionally from the caffeine as well as the ergotamine, and not as effective for headache as rectal or parenteral therapy. The dose is 1 to 6 tablets.

Ergotamine tartrate, 1 mg., caffeine, 100 mg., acetophenetidin, 130 mg., and belladonna alkaloids 0.1 mg. (Wigraine): an uncoated tablet for oral use, which is reported to dissolve quickly. This is a new product that bears promise and deserves more extensive trial.

Ergotamine tartrate 0.3 mg., bellafoline 0.1 mg., and phenobarbital, 20 mg. (Bellergal): a tablet for oral use containing so little ergotamine that it is rarely useful in the acute attack. Occasionally, however, it may be a well tolerated adjunct to other therapy in patients who cannot use larger amounts, and it has a place in the treatment of attacks in children. Its prophylactic administration is discussed below.

Suppositories for rectal administration, containing ergotamine tartrate, 2 mg., and caffeine alkaloid 100 mg. (Cafergot suppositories)*: this route has made it possible to stop headache more reliably,

*Many workers have incorporated other drugs in suppositories of this sort. These include atropine derivatives, antihistaminics, such as Benadryl and Dramamine, sedatives and analgesics. One such combination suppository that has met with particular success is that described by Ryan.[32] This contains ergotamine tartrate, 2 mg., caffeine 100 mg., bellafoline 0.25 gm., and pentobarbital sodium, 60 mg. A suppository of this composition is now on the market under the trade name of Cafergot PB suppositories. Undoubtedly, various combinations can be tailored to suit individual needs.

with less ergotamine and with fewer unpleasant side effects than with oral medication. In my opinion the dose included in the suppository is usually more than is necessary. An initial trial with half a suppository is recommended.

Ergotamine tartrate for parenteral use in ampoules containing 0.25 mg. (0.5 cc.) and 0.5 mg. (1 cc.) (Gynergen), for subcutaneous, intramuscular or intravenous use: this is the backbone of treatment for the migraine attack. It stops the headache most reliably and in the highest percentage of cases. Unpleasant side effects are not uncommon but may be reduced by the finding of the minimal effective dose. It is the drug of choice for helping to establish the diagnosis of migraine. Ergot therapy of migraine should not be discarded as a failure until it has been given, early in an attack, since patients will respond to this when other forms of ergot administration have failed. The subcutaneous and intramuscular routes of administration are recommended except for exceptional emergencies, when the intravenous route may be used; blood-pressure elevation and vascular effects in general are distinctly more marked when the intravenous route is used, and should be borne in mind.

Dihydroergotamine methanesulfonate, containing 1 mg. in a 1-cc. ampoule for subcutaneous, intramuscular and intravenous use (Dihydroergotamine or D.H.E. 45): this dihydrogenated form of ergot alkaloid has come into popular use because some patients have been found to tolerate it better than ergotamine tartrate. Milligram for milligram it is only about a half to a fourth as effective as ergotamine tartrate in stopping headache. Undoubtedly, some patients can find relief for their headache without unpleasant side effects from D.H.E. 45 who cannot find a dose of ergotamine tartrate that will serve them as well. Some of these patients, however, have not experimented sufficiently to find the minimal dose of ergotamine tartrate that is required for them. In such cases further trial of reduced dosage of ergotamine tartrate reveals that headache can be relieved without side effects by this drug as well as by D.H.E. 45. In others Dihydroergotamine is the only drug that can be tolerated. In general it is a very effective and useful agent. The route of administration is the same as that for ergotamine tartrate.

TABLE 1. *Doses of Various Ergot Derivatives.*

NAME OF COMMERCIAL PRODUCT	COMPOSITION	FORM	ROUTE	USUAL INITIAL DOSE	MAXIMUM INITIAL DOSE	MAXIMUM DAILY AMOUNT
Gynergen	Ergotamine tartrate, 1 mg.	Tablet	Oral	1-3 tablets	5 tablets	10 tablets
Bellergal	Ergotamine tartrate, 0.3 mg.; bellafoline 0.1 mg.; phenobarbital, 20 mg.	Tablet	Oral	1-3 tablets	4 tablets	6 tablets
Cafergot	Ergotamine tartrate, 1.0 mg.; caffeine, 100.0 mg.	Tablet	Oral	1-2 tablets	3 tablets	6 tablets
Wigraine	Ergotamine tartrate, 1.0 mg.; caffeine, 100.0 mg.; acetophenetidin, 130.0 mg.; belladonna alkaloids, 0.1 mg.	Tablet	Oral	1-2 tablets	3 tablets	6 tablets
Cafergot suppositories	Ergotamine tartrate 2.0 mg.; caffeine 100.0 mg.	Rectal suppository	Rectal	½-1 suppository	1 suppository	2 suppositories
Cafergot PB suppositories	Ergotamine tartrate 2.0 mg.; caffeine 100.0 mg.; bellafoline 0.25 mg.; pentobarbital 60.0 mg.	Rectal suppository	Rectal	½-1 suppository	1 suppository	2 suppositories
Gynergen	Ergotamine tartrate; 0.5 mg. per cc.	Ampoules (0.5 & 1 cc.)	Subcutaneous & intramuscular	0.3 cc.-1.0 cc.	1.0 cc.	1.5 cc.
			Intravenous	0.3 cc.-0.5 cc.	0.5 cc.	1.0 cc.
Dihydroergotamine D.H.E. 45	Dihydroergotamine Methane sulfonate; 1 mg. per cc.	Ampoules	Subcutaneous & intramuscular	0.75-1.0 cc.	1.5 cc.	3.0 cc.
			Intravenous	0.5 cc.	0.75 cc.	1.0 cc.

Toxic effects, amount and frequency of dosage of ergot alkaloids in the therapy of migraine. A healthy respect for the toxic properties of ergot derivatives has arisen in the minds of most physicians because of the well known "spontaneous" epidemics of ergotism in France and Germany that have occurred from widespread consumption of "poisoned rye" and the reported cases of ergotism that have arisen during the course of intentional ergot therapy for a number of medical disorders. Such caution is commendable, but it should not be allowed to preclude the relief that ergot may bring to many migraine sufferers when it is used properly, within the limits of knowledge of its dangers, effectiveness and shortcomings. Pertinent facts to be gleaned from the literature and the experience of those most versed in the use of these drugs for migraine may be grouped as follows:

In the reported epidemics of ergotism resulting from ingestion of rye "poisoned" by the fungus *Claviceps purpurea,* symptoms of two general types are described — namely, those primarily affecting the central nervous system and causing convulsions and those related to tissue necrosis and ischemia resulting from peripheral vasoconstriction. Evidence of more widespread toxicity has occurred in

a few cases of massive overdosage with extracts or powder of whole ergot.[33] These patients present such symptoms as headache, nausea and vomiting, tinnitus, blurred vision, unconsciousness, convulsions, anuria, hemorrhagic colitis, subcutaneous hemorrhages and jaundice.

However, the reported serious toxic effects of the refined alkaloid, ergotamine tartrate, are related, with a few exceptions that may be classified under the heading of a drug idiosyncrasy,[33] to the capacity of this drug to produce prolonged and marked vascular constriction, with resulting tissue ischemia and, in some cases, thrombosis and gangrene. The symptoms and signs arising from such vasoconstriction are muscle cramps, joint pains, paresthesias, coldness of the extremities, intermittent claudication, elevation of blood pressure, pulselessness, pallor, cyanosis, thrombophlebitis, peripheral arterial thrombosis and gangrene, precordial pain, abdominal pain and coronary-artery and cerebral-artery thrombosis. Other symptoms that may or may not be related to vascular constriction include nausea, vomiting (common) and cardiac arrhythmias (rare).[34] Painful uterine contractions, owing to the oxytocic principle present in ergotamine tartrate (but not present in Dihydroergotamine), are sometimes experienced. Other bizarre symptoms, such as choking sensations, globus abdominalis, anxiety, restlessness, insomnia, itching and urticaria,[35] present themselves very rarely, and their mechanism remains unexplained. Since it becomes apparent from the conditions mentioned above that the main threat arising from ergotamine therapy is that of tissue ischemia secondary to vasoconstriction, a list of contraindications to its use may be derived from both practical experience and theoretical considerations.

Contraindications

Known and suspected vascular disease. In addition to manifest vascular disorders, such as Raynaud's disease, Buerger's disease, periarteritis, cranial arteritis, arteriosclerosis, hypertensive cardiovascular disease, coronary-artery disease, syphilitic arterial disease and thrombophlebitis, all of which become obvious contraindications to a vasoconstrictive drug, one should bear in mind the possibility of hidden vascular disorders in the peripheral, coronary and cerebral arterial systems in patients beyond middle age. In this older group of patients ergot derivatives should be used with the utmost caution, if at all. (Patients who have taken ergotamine with impunity over the years, however, do not need to abandon its use just because they have attained middle age.) Several examples of the development of precordial pain and rare cases of coronary thrombosis and death after the injection of a standard dose of ergotamine are available in the literature. Most of these were in patients who were known to have organic cardiovascular disease and who in the light of present knowledge would not have received ergotamine.[36-38] Occasional patients, however, have suffered anginal pain (in 1 case electrocardiographic changes consistent with coronary thrombosis developed) in whom no obvious contraindication to ergot therapy provided a warning.[39] Strong evidence that the intravenous use of ergotamine is particularly likely to produce coronary symptoms is apparent in these reports.

Peters and Horton[40] describe phlebothrombosis in a twenty-seven-year-old nurse after the excessive use of Dihydroergotamine; recurrence of this disease after a free interval of a year followed two more injections of Dihydroergotamine.

Jaundice and liver disease. Ergotamine was at one time extensively used as an effective remedy for the itching of jaundice. It soon became evident, however, that liver disease rendered patients more vulnerable to the toxic effects of ergot. Several reports[33,41-43] indicate that, whereas many subjects with liver disease can tolerate reasonable amounts of ergotamine, a few become extremely susceptible to small doses. Consequently, its use in the face of jaundice seems unwise unless extreme precautions are observed. Fortunately, liver disease frequently serves to ameliorate migraine, thus rendering the use of ergot derivatives less necessary.

Puerperal sepsis, avitaminosis, cachexia and anemia. On review of the literature for reported examples of ergotism it becomes apparent that the conditions noted above may play an important contributing part in the development of susceptibility to ergot. von Storch,[35] in 1938, collected 23 cases of ergotism arising in gynecologic and obstetric patients, in 16 of whom there was accompanying sepsis. Since this condition in itself is conducive to vascular thrombosis the added danger deriving from the use of ergot should be avoided. The presence of avitaminosis and cachexia in populations suffering from epidemics of ergotism and a few cases in which debilitated patients have suffered major reactions to ergot[44] suggest that great caution should be observed in the treatment of such persons. Since the fundamental difficulty in ergot poisoning is tissue ischemia the presence of anemia may accentuate the anoxemia produced by vasoconstriction.

Thyrotoxicosis. Ergotamine was at one time widely used as a treatment for thyrotoxicosis, and the frequency of its use for this purpose may account for the fact that von Storch[35] was able to collect 11 examples of ergot poisoning among thyrotoxic patients in 1938. A particular case is worth noting.[45] A forty-nine-year-old woman with a basal metabolic rate of +106 per cent and atrial flutter suffered severe, repeated and prolonged precordial pain after a single injection of 0.5 mg. of ergotamine tartrate intramuscularly, and died two days later of cerebral thrombosis. Thyrotoxicosis, with its increased tissue demands for oxygen, relative avitaminosis, cardiac irregularities and cachexia, may well render the patient more susceptible to the effects of ergot.

Pregnancy. Because of the oxytocic principle present in ergotamine tartrate it should not be used in patients who are pregnant or who desire particularly to become pregnant. Since Dihydroergotamine does not contain the oxytocic factor it may be used instead.

If the contraindications listed above are borne in mind, the more serious consequences of ergot therapy will be avoided. There remains, however, a great variation in ability to tolerate these drugs without the development of transient or prolonged symptoms of ergot toxicity. Thus, one patient may experience no untoward symptoms from a standard dose, but another may manifest so many of the transitory unpleasant side effects (such as nausea, vomiting, muscle cramps and prostration) that the cure becomes worse than the disease. This fact makes it important for the patient and the physician to initiate therapy with caution and to experiment with the dosage so as to find the amount of ergot that produces for that person the best ratio of effectiveness to toxicity. The smallest amount of ergotamine that is effective in relieving the headache within a reasonably satisfactory period (three hours) should be determined. If prohibitive toxic symptoms still persist at this dosage level, an attempt should be made to combat them by the use of other drugs, or a trial of Dihydroergotamine should be made. The nausea and vomiting caused by ergotamine therapy can often be successfully offset by the administration, preferably in advance of the ergot, of atropine derivatives, Dramamine, Benadryl or chlorpromazine. Calcium gluconate was reported by O'Sullivan[31] as being specific for muscle cramps. It has been my experience that cortisone, in doses ranging from 25 to 150 mg., taken before and during the course of a headache and its treatment by ergotamine, has been effective in some cases in preventing nausea and vomiting, alleviating prostration and fatigue and in getting the patient over the whole experience with less misery. Although Dihydroergotamine is less effective in stopping headache than ergotamine itself, some patients find that they can tolerate it much better and derive, in general, a more satisfactory result.

Not only do patients vary in their tolerance to a single dose of the ergot drugs but also there is a great difference in tolerance to the long-term effects of ergot therapy. Until recent years most authors have advised against the use of these drugs more than twice a week for fear of the development of symptoms of ergotism. Many examples may now be cited, however, to illustrate the fact that certain persons may take large amounts of these drugs daily over periods of months and years without demonstrable harm.[46-50]

Development of ergotism in the course of "standard" migraine therapy has been reported in several cases.[40,51-57] I know of 2 others. In these cases the symptoms of numb, painful, cold, cyanotic extremities were usually present for a considerable period and might well have forewarned the properly instructed patient or doctor of imminent danger. In 2 patients gangrene of one or more toes developed. In all the others restoration of function and regression of symptoms followed removal of the drug and institution of measures to bring about vasodilatation. In 3 cases ergotism occurred within a short period (two or three weeks) of excessive ergot intake (1 cc. of D.H.E. 45 every four hours; 6 Cafergot tablets daily; and 0.5 cc. of Gynergen every four to six hours). In the others longer periods of months or years had been spent in daily injection or ingestion of ergot — for example, 518 mg. by mouth in fifteen weeks, 1529 mg. subcutaneously over ten years and 0.5 mg. intramuscularly each day for two years.

Oddly enough, the only reported fatal cases of ergot poisoning occurring in the course of migraine therapy have been those of physicians who took "unreasonable" amounts of ergotamine.[50,58] The doses recorded for 2 of these unwise doctor patients were 3 mg. and 3.2 mg. of ergotamine tartrate administered in one dose intravenously.

Lennox,[24] Peters and Horton,[40] Silfverskiöld[54a] and, more recently, Friedman and von Storch[54b] have pointed out that frequent doses of ergot, although they stop the headache of the moment, tend to foster the development of the next headache, an observation with which my experience is in agreement. Whether this phenomenon is due to vasodilatation and headache that develop as an aftermath or late reaction to the vasoconstriction caused by the ergot or to the fact that patients so relieved of their headache fail to take the rest and observe the fundamental rules of living that are necessary for the successful over-all treatment of their disease, or both, remains a question. Withdrawal of ergot, usually under hospital conditions, and substitution of other forms of therapy (as mentioned below) seem indicated if the patient can be persuaded to comply; otherwise, it may be justifiable to prescribe a small dose of ergot at bedtime each night rather than to require the patient to wait for the onset of headache and the need for an even larger dose. Such situations are far from desirable and probably represent a failure in the general care of the patient, but they do exist. If every effort has been made to forestall them and they nevertheless develop, it may be well to remember that in most patients no serious harm takes place, close observation can prevent serious symptoms of ergot toxicity and at least chronic invalidism or addiction to even more dangerous drugs is avoided. Certainly, if symptoms of impending ergotism develop, withdrawal of the drug must be insisted upon, and once they have actually set in, the added use of vasodilators, such as alcohol,[33] nicotinic acid, papaverine[51] and (theoretically) short-term anticoagulants, such as heparin, seems indicated.

By and large, patients do not become resistant to ergot derivatives or, if they do, to a very slight degree. Occasional cases of resistance have been reported,

but they are rare.[54b,59] Recently, I received a letter from a patient who stated that since 1937 he had treated 2000 headaches with ergotamine tartrate. Never, in that time, had 0.4 cc. of ergotamine tartrate, given subcutaneously, failed to bring relief in twenty minutes. It should be remembered that variation in the severity of headache over the years may account for some cases of seemingly increased tolerance.

From the foregoing it may be deduced that the frequency of use of ergot alkaloids is an individual matter and requires tailoring to suit the individual needs and tolerance. From my experience and the reports in the literature it appears that serious symptoms of prolonged ergot therapy will not develop in a patient who is free of the recorded contraindications and who tolerates a single dose well, and if provision is made for each week of treatment to contain at least two days in which no ergot is administered.

Principles in Use of Ergot Derivatives

From the material already presented certain principles may be evolved:

The patient should be checked regarding the diagnosis of migraine and possible contraindications to ergot therapy.

The ergot drug to fit the needs of the patient should be carefully selected, the dosage adjusted to the minimal effective amount, and the side effects combated by suitable adjuvant drugs.

The patient should be instructed to use ergot as early in the attack as he can make the diagnosis of "one of his migraines." (Once the amount of ergot that is required for his attacks has been determined, he should be urged to use that amount at the start rather than to distribute it over several hours.)

He should be warned of possible side effects, and at the same time told that they usually can be successfully combated if they occur. (An unexpected bad reaction destroys the patient's confidence in both medicine and doctor.)

Ergot derivatives should not be considered a failure until ergotamine tartrate has been given, early in an attack, by the parenteral route.

The schedule should be lightened on the day of a headache, even if relief has been produced by ergotamine.

Regarding the amount and frequency of dosage of ergot derivatives, the data presented in Table 1 are offered for use as a guide.

Intravenous administration should be avoided except in rare emergencies when the patient's tolerance is well understood.

There should be at least two days in each week when no ergot is used.

If symptoms of toxicity of more than a transitory nature begin to appear, ergot should be stopped at once.

Other Therapy Useful in the Acute Attack of Migraine

In the hands of various workers and in certain patients the following drugs have proved useful in the treatment of the headache of migraine (they have not been as effective as ergot in the relief of migraine headache, but may prove useful for the patients who cannot take ergot derivatives):

Methyl-iso-octenylamine (Octin Hydrochloride).[60] This drug acts in some patients as a vasoconstrictor and in such cases may prove useful in stopping headache. Because of its tendency to cause transitory hypertension a trial dose of 50 mg. intramuscularly should first be administered, and the blood pressure checked. Provided no alarming hypertension results, this drug may be used in a dose of 50 to 200 mg. intramuscularly. Oral and rectal administration of Octin, for the acute attack, is rarely effective. Octin should not be given in hypertension, but may be used during pregnancy. MacNeal[61] reports that a combination of 50 mg. of Octin and 1 cc. of D.H.E. 45 is very effective.

Sodium nicotinate.[62] An occasional patient is relieved of headache after the careful intravenous administration of sodium nicotinate in doses ranging from 25 to 100 mg. The inconvenience of this form of therapy, its unreliability and the unpleasant vasodilatation that accompanies its administration greatly limit its usefulness.

Antihistaminics. The oral or parenteral administration of various antihistaminics has proved beneficial in the treatment of the acute migraine attack in some cases. The most enthusiastic report in this field is that in which Vaisberg[63] records universal success in treating 100 attacks of migraine in 50 patients by intravenous or intramuscular injection of 50 to 100 mg. of "Dramamine Injectable." Drowsiness caused by this drug was offset, as necessary, by oral use of amphetamine. Vaisberg also states that the parenteral use of chlorpromazine has been similarily effective. My experience suggests that the last drug has been helpful in alleviating nausea and vomiting but in many cases has not stopped headache.

Thiamine chloride. Palmer has reported the successful termination of migraine attacks by the intravenous administration of 120 to 180 mg. of thiamine chloride.

Steroid hormones. ACTH in doses ranging from 25 to 100 mg. intramuscularly and cortisone by mouth in doses from 50 to 200 mg. have been used with apparent effect in several isolated cases. In other patients headache has not been relieved, but recovery from the whole exhausting experience has been enhanced.

Miscellaneous measures. Inhalation of 100 per cent oxygen,[65] inhalation of triethylene, injection of epinephrine, Pituitrin and nor-epinephrine and oral administration of amphetamine compounds

and ephedrine are occasionally of benefit, but usually prove either so inconvenient or so unreliable that their usefulness is very limited. In certain patients in whom the headache is localized in the region of the temporal artery, injection of procaine in the region of the artery anterior to the ear affords relief.[66]

Physical measures. The application of an ice cap to the head or heat to the neck, a Turkish bath or tepid tub bath or hot mustard foot bath all may at times be of some benefit, and at times neck traction and massage may help to relieve painful muscle spasm associated with the headache.

Cerebral vasodilators (for "classic" migraine). Nitroglycerin, amyl nitrite, inhalation of 10 per cent carbon dioxide, nicotinic acid and sympatholytic drugs have been used at the very onset of "classic" migraine, in the hope that relief of the vasoconstriction that is supposedly responsible for the visual scotomas, hyperesthesia and so forth will abort this phase and its painful sequelae. Under laboratory conditions the use of carbon dioxide has accomplished this,[67] but it is not a practical measure in daily life. Small doses, such as 0.3 mg. (1/200 gr.), of nitroglycerin or inhalation of amyl nitrite has definitely proved useful to a few patients. The effect of 100 mg. of nicotinic acid orally or of sympatholytic drugs (Hydergine, Priscoline and so forth) is of questionable benefit. Success in abolishing the preheadache phenomena by these means is so spotty that most patients find it wise to fortify their cranial vessels against the painful secondary vasodilatation by the immediate use, at the onset of the attack, of their favorite vasoconstrictor.

(To be concluded)

References

16. Wolff, H. G. *Headache and Other Head Pain.* 642 pp. New York: Oxford University Press, 1948. Pp. 352 and 356.
17. Eulenburg, A. Subcutane Injectionen von Ergotinin-(Tanret): Ergotinum citricum solutum (Gehe). *Deutsche med. Wchnschr.* **9**:637-639, 1883.
18. Thompson, W. H. Ergot in treatment of periodic neuralgias. *J. Nerv. & Ment. Dis.* **21**:124-126, 1894.
19. Stoll, A. Zur Kenntnis der Mutterkornalkaloide. *Verhandl. d. Schweizer. naturf. Gesellsch.* **101**:190, 1920.
20. Maier, H. W. L'ergotamine, inhibiteur du sympathique étudié en clinique, comme moyen d'exploration et comme agent thérapeutique. *Rev. neurol.* **1**:1104-1108, 1926.
21a. Tzanck, M. A. Le traitement des migraines par le tartrate d'ergotamine. *Bull. et mém. Soc. méd. d'hôp. de Paris* **52**:1057-1061, 1928.
21b. Cornil, M. Sur l'action favorable du tartrate d'ergotamine dans un cas de migraine rebelle. *Rev. Méd. de l'Est.* **55**:153, 1927.
22. Trautmann, E. Die Beeinflussung migräneartiger Zustände durch ein sympathikushemmendes Mittel (Gynergen). *München. med. Wchnschr.* **75**:513, 1928.
23. Ignelzi, L. G. Migraine: comparatively new approach as to therapy. *M. J. & Rec.* **135**:447, 1932.
24. Lennox, W. G. Use of ergotamine tartrate in migraine. *New Eng. J. Med.* **210**:1061-1065, 1934.
25. Brock, S., O'Sullivan, M., and Young, D. Effect of non-sedative drugs and other measures in migraine: with especial reference to ergotamin tartrate. *Am. J. M. Sc.* **188**:253-260, 1934.
26. Logan, A. H., and Allen, E. V. Treatment of migraine with ergotamine tartrate. *Proc. Staff Meet., Mayo Clin.* **9**: 584-588, 1934.
27. Solomon, P. Sympathetic nervous system in migraine: negative effect of ergotamine tartrate on electrical resistance of skin during relief of migraine headache. *Arch. Neurol. & Psychiat.* **35**: 964-974, 1936.
28. Bluntschli, H. J., and Goetz, R. H. Effect of ergot derivatives on circulation in man with special reference to two new hydrogenated compounds (dihydroergotamine and dihydroergocornine). *Am. Heart J.* **35**:873-894, 1948.
29. Bercel, N. A. Treatment of migraine: results with dihydroergocornine methane sulfonate (DHO-180) and other derivatives. *California Med.* **72**:234-238, 1950.
30. Pool, J. L., and Nason, G. I. Cerebral circulation: XXXV. Comparative effect of ergotamine tartrate on arteries in pia, dura and skin of cats. *Arch. Neurol. & Psychiat.* **33**:276-282, 1935.
31. O'Sullivan, M. E. Termination of one thousand attacks of migraine with ergotamine tartrate. *J.A.M.A.* **107**:1208-1212, 1936.
32. Ryan, R. E. Headache: otoryngologist's viewpoint of differential diagnosis and treatment of certain types. *J. Missouri M. A.* **49**:899-902, 1952.
33. Comfort, M. W., and Erickson, C. W. Untoward effects from use of ergot and ergotamine tartrate. *Ann. Int. Med.* **13**:46-60, 1939.
34. Carter, J. B. Cardiac manifestations following ergotamine tartrate therapy for migraine. *J.A.M.A.* **114**:2298, 1940.
35. von Storch, T. J. C. Complications following use of ergotamine tartrate (ergot preparation): their relation to treatment of migraine headache. *J.A.M.A.* **111**:293-300, 1938.
36. Master, A. M., Pordy, L., Kolker, J., and Blumenthal, M. J. "Two-step" exercise electrocardiogram in functional heart disturbances and in organic heart disease: use of ergotamine tartrate. *Circulation* **1**:692-699, 1950.
37. Scherf, D., and Schlachman, M. Electrocardiographic and clinical studies on action of ergotamine tartrate and dihydro-ergotamine 45. *Am. J. M. Sc.* **216**:673-679, 1948.
38. McNerney, J. J., and Leedham, C. L. Acute coronary insufficiency pattern following intravenous ergotamine studies. *Am. Heart J.* **39**:629-632, 1950.
39. Fuchs, M., and Blumenthal, L. S. Use of ergot preparations in migraine. *J.A.M.A.* **143**:1462-1464, 1950.
40. Peters, G. A., and Horton, B. T. Headache: with special reference to excessive use of ergotamine preparations and withdrawal effects. *Proc. Staff Meet., Mayo Clin.* **26**: 153-161, 1951.
41. Lichtman, S. S. Clinical experience with ergotamine tartrate. *J.A.M.A.* **107**:148, 1936.
42. Yater, W. M., and Cahill, J. A. Bilateral gangrene of feet due to ergotamine tartrate used for pruritus of jaundice. *J.A.M.A.* **106**:1625-1631, 1936.
43. Gould, S. E., Price, A. E., and Ginsberg, H. I. Gangrene and death following ergotamine tartrate (gynergen) therapy. *J.A.M.A.* **106**:1631-1635, 1936.
44. Zimmerman, O. Störung der Coronardurchblutung durch Ergotamin. *Klin. Wchnschr.* **14**:500-503, 1935.
45. Labbé, M., Boulin, R., Justin-Besançon, and Gouyen. L'angine de poitrine ergotaminique. *Presse méd.* **37**:1069, 1929.
46. King, G. S. Headaches and their treatment. *New York State J. Med.* **51**:255-259, 1951.
47. Sangiorgi, M. Sugli effeti della terapia ergotaminica prolungata: (studio clinico di un caso di trattamento ergotaminico abnormemente protratto e non seguito da complicanze tossiche). *Riforma med.* **65**:4-9, 1951.
48. Alvarez, W. C. What to do in rebellious case of migraine: list of drugs being used today. *Gastroenterology* **9**:754-764, 1947.
49. Blamoutier, P. Le tartrate d'ergotamine: médication préventive de la migraine ophthalmique. *Presse méd.* **52**:164, 1944.
50. Lennox, W. G. *Festschrift für Herrn Professor Dr. Arthur Stoll.* 665 pp. Basel: Benno Schwabe, 1947. Pp. 363-372.
51. Thompson, W. S., Jr., McClure, W. W., and Landowne, M. Prolonged vasoconstriction due to ergotamine tartrate: report of case with evaluation of recovery with objective vascular findings. *Arch. Int. Med.* **85**:691-698, 1950.
52. Cleveland, F. E., and King, R. L. Gangrene following ergotamine tartrate therapy of migraine. *Bull. Mason Clin.* **2**:19-26, 1948.
53. Isenstead, J. H. Instance of ergotism. *Mod. Med.* **16**:19-22 (September), 1948.
54a. Silfverskiöld, B. P. Gynergen abuse in cases of migraine. *Acta psychiat. et neurol.* **46**(Supp.):281-285, 1947.
54b. Friedman, A. P., and von Storch, T. J. C. Ergotamine tolerance in patients with migraine. *J.A.M.A.* **157**:881-884, 1955.
55. Hjertaas, A. Peripheral circulatory disturbances after gynergen therapy. *Nord. med.* **37**:481-483, 1948.
56. Soltz, S. E., Brickner, R. M., Riley, H. A., and Salmon, L. A. Use of orally administered ergotamine tartrate, amniotin, and phenobarbital in treatment of migraine. *Bull. Neurol. Inst. New York* **4**:432-441, 1935.
57. Martinetti, R. Terapia delle cefalee. *Recenti progr. med.* **6**:527-546, 1949.
58. Jervis, G. A., and Kindwall, J. A. Schilder's disease in ergotamine intoxication. *Am. J. Psychiat.* **98**:650-655, 1942.
59. Wolfson, W. Q., and Graham, J. R. Development of tolerance to ergot alkaloids in patient with unusually severe migraine. *New Eng. J. Med.* **241**:296-298, 1949.
60. Peters, G. A., and Zeller, W. W. Evaluation of new agent (methyl-iso-octenylamine) in treatment of vasodilating headaches. *Proc. Staff Meet., Mayo Clin.* **24**:565-568, 1949.
61. MacNeal, P. S. Symposium on acute medical emergencies: headache as emergency complaint. *M. Clin. North America* **33**:1581-1596, 1949.
62. Goldzieher, J. W., and Popkin, G. L. Treatment of headache with intravenous sodium nicotinate. *J.A.M.A.* **131**:103-105, 1946.
63. Vaisberg, M. Dramamine (injectable) in migraine: preliminary report. *Ann. Allergy* **12**:180, 1954.
64. Palmer, H. D. Treatment of migraine with vitamin B_1: résumé of one year's experience. *Arch. Neurol. & Psychiat.* **45**:368-371, 1941.
65. Alvarez, W. C., and Mason, A. Y. Results obtained in treatment of headache with inhalation of pure oxygen. *Proc. Staff Meet., Mayo Clin.* **15**:616-618, 1940.
66. Patzer, R., Derbes, V., and Engelhardt, H. Periarterial infiltration in diagnosis and treatment of migraine: experimental and clinical experiences with eucupine and procaine hydrochloride. *Arch. Surg.* **59**:296-300, 1945.
67. Schumacher, G. A., and Wolff, H. G. Experimental studies on headache: A. Contrast of histamine headache with headache of migraine and that associated with hypertension. B. Contrast of vascular mechanisms in preheadache and headache phenomena of migraine. *Arch. Neurol. & Psychiat.* **45**:199-214, 1941.

MEDICAL INTELLIGENCE

LOCAL TETANUS*

Report of a Case Involving the Left Facial Muscles

E. CONVERSE PEIRCE, II, M.D.,† AND
C. HARWELL DABBS, M.D.‡

KNOXVILLE, TENNESSEE

TETANUS is caused by a potent toxin of *Clostridium tetani*, produced locally in a wound and disseminated by lymphatics and by the blood stream.[1] The toxin acts directly on muscle and causes a contraction that is unaccompanied by nerve-action current and persists after the nerve is severed. Spasms tend to occur first in muscles near the site of toxin production, but later there is widespread muscle involvement.[2] When the case is severe there are usually marked muscle spasms, with contraction of the muscles of mastication (trismus), facial spasm (risus sardonicus), opisthotonos and generalized convulsions.

Tetanus that remains localized is decidedly rare although cases are included in some of the larger series.[3,4] Green[2] found 17 cases reported in about a twenty-year period, but in all these generalized tetanus eventually developed. It has not been possible to find a report of tetanus limited to the muscles of one side of the face in the available literature. The present case emphasizes the importance of recognizing tetanus early by a search for local signs. It produced a striking picture and, if it had not been quickly differentiated from intracranial injury, might well have proved fatal to the patient. For these reasons a report seems desirable.

CASE REPORT

An 8-year-old boy was first seen in the office late in the morning of January 15, 1955, with a history of having been struck with a stick on the left aspect of the scalp 2 days before by another boy while playing. The family had noted swelling of the periorbital tissues and also that his mouth pulled to the left side of his face. There was no history of unconsciousness, dizziness, headache, loss of appetite or any other symptom. There had been no previous known facial asymmetry. The temperature was 99.8°F. After matted hair over the laceration, which lay just within the hairline above and lateral to the outer aspect of the left eye had been shaved off, a 1-cm.-long, deep perforation filled with thick pus but with little surrounding inflammation was seen. There was a definite facial asymmetry, which was thought by 2 examiners to constitute a right-sided facial weakness. The remainder of the examination, including a careful neurologic investigation, was within normal limits. Skull films were negative for fracture. He was given 300,000 units of penicillin and admitted to the Crippled Children's Hospital for observation of possible head injury or infection.

On admission to the hospital the following additional history was obtained. The patient had had German measles and chicken pox. He had had no operations or serious injuries. He had not been immunized with tetanus toxoid.

Physical examination showed a definite facial asymmetry, which was now seen to be a left-sided spasm rather than weakness on the right. The left palpebral fissure was narrowed because of spasm of the orbicularis muscle, which drew down the eyebrow despite spasm of the frontalis muscle. The corner of the mouth was drawn over to the left, and the nasolabial crease was definitely deepened.

FIGURE 1. *Appearance of the Patient on the Day of Diagnosis.*

Both voluntary and involuntary contraction leads to accentuation of the asymmetry.

Involuntary spasm of this side of the face was produced when a bright light was flashed in the patient's face (Fig. 1). There was a positive Chvostek sign, with spasm of both the orbicularis and perioral muscles. The neck was supple, and there was no trismus or muscle spasms anywhere else in the body. The remainder of the examination was unremarkable.

The temperature was 100°F. by rectum. The pulse and respirations were normal.

Urinalysis was within normal limits. The white-cell count was 9950, with 72 per cent neutrophils, 25 per cent lymphocytes and 3 per cent monocytes, and the hemoglobin 13 gm. per 100 cc. A swab culture taken from the puncture wound on the day of admission grew out *Escherichia coli*. Cultures of excised tissue on January 18 grew out *Cl. histolyticum* and a bacillus of the morphology of *Cl. tetani*. Later a nonhemolytic streptococcus and *Micrococcus pyogenes* were isolated.

A tentative diagnosis of localized tetanus was made within 2 hours of admission, and 20,000 units of tetanus antitoxin was given intramuscularly; 40,000 units was given on the following day, followed by 20,000 units daily until January 21, when it was reduced to 1 dose every 3 days. Penicillin, 300,000 units, was given twice daily until January 22 and then daily; 0.5 gm. of streptomycin was administered twice daily until January 22. The wound was treated with hydrogen peroxide irrigations until January 22, zinc peroxide not being obtainable. Later on January 17 the patient was noted to have a definite trismus but this escaped our attention until the following day. Because of this progression the wound was excised under local anesthesia. A few small particles of foreign material were seen, but there was no

*From the Department of Surgery, Acuff Clinic.

†Surgeon-in-chief, Acuff Clinic; attending surgeon, East Tennessee Crippled Children's Hospital.

‡Medical director and member, Department of Surgery, Acuff Clinic; attending surgeon, East Tennessee Crippled Children's Hospital.

evidence of suppuration. D-tubocurarine in doses of 12 to 50 mg. was tried for the trismus, without noticeable effect. Fortunately he was always able to open his mouth about 1 cm. or so and consequently was able to eat. The trismus continued unchanged until about January 27 and then gradually improved. Some spasm of the jaw muscles was still present on February 2, the day of discharge, all medications having been discontinued on February 1. After discharge he was seen at intervals in the office, with no evidence of recurrence or development of serum sickness. Several weeks later there was still a persistent narrowing of the left palpebral fissure.

Discussion

When symptoms begin as early as two or three days after injury the mortality rate in tetanus approaches 100 per cent even when vigorous therapy is given.[5] In the case reported above, the muscles involved changed the patient's expression and so were noticed much earlier than a spasm of the leg muscles, the arm muscles or the abdominal muscles would have been. This case is a clear reminder that tetanus must always be considered when localized muscle spasm is a presenting feature. Otherwise, mild dysphagia, a limp, tightness of the abdominal muscles or slight ataxia can easily be discounted. Of 352 patients with tetanus seen at the Charity Hospital in New Orleans, 12 were sent home although they had one or more important signs or symptoms of tetanus; 14 were admitted and treated for one to seven days with some other diagnosis.[6] These delays in effective antiserum treatment doubtless contribute to the over-all mortality of about 45 per cent.

In the case reported above, it was not necessary to use any anticonvulsants, nor did we deem it advisable to give ACTH or cortisone. Use of reasonably sized doses of a curare preparation apparently had little effect, and this is in keeping with cases showing generalized convulsions. It is noteworthy that two clostridia were grown from the patient's wound three days after the start of adequate antibacterial therapy. It seems reasonable to perform wound excisions early whenever possible.

It is of interest that a case of tetanus apparently does not confer immunity.[7] To be protected in the future this patient will require the usual toxoid administration. This was not done at the time of admission because it was believed that the large doses of antitoxin given might neutralize the toxoid and prevent him from obtaining a solid immunity.[8] There is evidence that immunization can be carried out concurrently with treatment, however.[9]

Tetanus continues to be an important civilian disease despite the ready availability of a satisfactory immunization procedure. Toxoid can be given without danger, and a recall dose after more than ten years may be expected to be effective.[10] There are nevertheless approximately 500 deaths annually, and the incidence of the disease has decreased only in those who have been immunized with tetanus toxoid.[11] There were only 12 cases among nearly 3,000,000 United States Army and Army Air Corps men during World War II, but, except for the military group and the children who have had immunization shots, there has been little change in the pattern of the disease.[10] Simple use of tetanus antitoxin after an injury is not satisfactory because extremely superficial wounds that never come to a doctor's attention may result in the disease, and in severe wounds a single injection may not be sufficient. In addition reactions occur in 10 to 25 per cent of patients given tetanus antitoxin, and occasionally these reactions are serious.[11]

Summary

A case of tetanus involving only the left facial muscles is reported. Symptoms developed within forty-eight hours of injury but progressed very little after prompt antitoxin administration. *Clostridium tetani* was isolated three days after administration of antibiotics was begun. The persistence of this disease despite the availability of adequate prophylaxis is pointed out, and a plea for more widespread immunization is made.

References

1. Abel, J. J., Evans, E. A., Jr., Hampil, B., and Lee, F. C. Researches on tetanus: toxin of Bacillus tetani is not transported to central nervous system by any component of peripheral nerve trunks. *Bull. Johns Hopkins Hosp.* **56**:84-114, 1935.
2. Green, C. C. Pathogenesis of local tetanus. *Ann. Surg.* **105**:998-1003, 1937.
3. Pratt, E. L. Clinical tetanus: study of 56 cases, with special reference to methods of prevention and plan for evaluating treatment. *J.A.M.A.* **129**:1243-1247, 1945.
4. Bruce, D. Tetanus: analysis of 1458 cases, which occurred in home military hospitals during years 1914-1918. *J. Hyg.* **19**:1-32, 1920.
5. Stone, W. J., and Hamilton, P. M. Tetanus. In *Nelson's Loose-Leaf Medicine*. Vol. 1. 617 pp. New York: Nelson, 1946. Pp. 463-469.
6. Vinnard, R. T. Three hundred and fifty-two cases of tetanus. *Surgery* **18**:482-492, 1945.
7. Batson, B., and Christie, A. Immunization: tetanus. *Pediat. Clin. North America* **1**:352, 1954.
8. Cooke, J. V., and Jones, F. G. Duration of passive tetanus immunity and its effect on active immunization with tetanus toxoid. *J.A.M.A.* **121**:1201-1209, 1943.
9. Miller, J. J., Jr., Ryan, M. L., and Beard, R. R. Speed of secondary immune response to tetanus toxoid with review of war reports and observations on simultaneous injection of toxoid and antitoxin. *Pediatrics* **3**:64-74, 1949.
10. Stafford, E. S., Turner, T. B., and Goldman, L. On permanence of anti-tetanus immunization. *Ann. Surg.* **140**:563-568, 1954.
11. Press, E. Desirability of routine use of tetanus toxoid. *New Eng. J. Med.* **239**:50-56, 1948.

DOCTORS AFIELD

Imhotep

William H. Sprunt, M.D.*

Chapel Hill, North Carolina

As man and god, more superlatives have been spoken and written of "Dr." Imhotep than of any physician who ever lived. In justification of this writing, one more can be added: Imhotep went farther afield than any physician has ever gone.

*Assistant professor of radiology, University of North Carolina School of Medicine.

Described by Osler as the "first figure of a physician to stand out clearly from the mists of antiquity," Imhotep lived about 3000 B.C., during the reign of King Zoser, an outstanding pharaoh of the Old Kingdom of Egypt. "In priestly wisdom, in magic, in the formulation of wise proverbs, in medicine and architecture, this remarkable figure . . . left so notable a reputation that his name was never forgotten."[1]

Within a hundred and fifty years of his death, Imhotep was worshiped extensively as a demigod. His rapid rise to popularity probably coincided with a religious revival occurring about 2850 B.C., when the common people began to find the gods of the rich and mighty too expensive in their sacrificial demands. It was natural for them to turn to the more economical and equally propitious worship of the demigods. Among these was the wise, skillful magician physician, who healed the sick, protected one from accident and gave children to the sterile.

For over two thousand years the worship of Imhotep persisted and was climaxed in 525 B.C. with his apotheosis to the rank of a full deity. He was then assigned a divine father, Ptah, one of the ancient Egyptian gods, to replace his earthly father, Kanofer, a noted architect. Deification of a mortal was rare in Egypt and is highly significant in an appraisal of Imhotep.

The Imhotep cult arose and flourished in Memphis, and there the ruins of one of the three temples known to have been erected solely in his name can still be seen. It became a famous hospital and school of medicine, named by the Greeks, the "Asklepieion." In addition to a small temple at Thebes, there was at Philae a larger structure, which has been extolled as a glorious example of Egyptian architecture. This was also used for clinical purposes thousands of years ago.

Over the door of the temple at Philae is an engraving placed there by the order of Ptolemy V Epiphanes, the same Ptolemy whose name was honored at one time by inscriptions, carved in basalt and placed in all the major temples of Egypt. The inscriptions were in three languages — Greek, Demotic (the running script or writing of the Egyptians of that day) and the sacred hieroglyphic symbols. Through one of the most fortunate coincidences in modern history, one of these stones was discovered and preserved by a soldier of Napoleon in 1798, as he was demolishing a wall near the village of Rosetta on the Nile delta.[2]

Twenty-four years later the great French scholar, Champollion, deciphered the hieroglyphics on the Rosetta stone and opened the door to the past of Egypt. Among the secrets revealed was the fact that the Greeks had adopted Imhotep into their own culture. They called him Imoutheses and assimilated him with their own Asklepios, in reality a Thessalian leech, whose importance in medicine seems to lie solely through his amalgamation with Imhotep. The Romans in turn adopted the Greek god of medicine and called him Aesculapius.

The medical profession is indebted to Dr. Jamison B. Hurry, a British physician, for his recognition and study of Imhotep.[3] Most of this material has been adapted from his monograph, including the subdivisions of Imhotep's versatile career: as vizier, as architect, as chief lector priest, as sage and scribe, as astronomer and as magician physician.

At the time of the Old Kingdom the vizier was chosen by the king because he was the wisest man in the land. The selection of Imhotep by Zoser was probably the best move Zoser ever made, for the two apparently were a perfect team, and during Zoser's reign the kingdom advanced considerably. As prime minister, or executive vice-president, the duties of the vizier were many, and they were vital to the country. He was bearer of the royal seal, chief priest, chief judge, overseer of the king's records, and supervisor of everything in the land, including the army, the navy, internal revenue and all the other departments of government that flourished then, even as today.

As architect and "chief of all the works of the king," Imhotep probably designed the famous "step-pyramid" of Sakkarah, called by Breasted[4] "the first large structure of stone known to history." The design of the pyramid was based on the mastaba, a flat-topped, oblong or rectangular structure, with sloping walls, built over the tombs of the wealthy. By the placing of six mastabas, one on top of the other and each a little smaller than the one below, a terraced, pyramidal structure was produced. It towered 195 feet into the air and measured 227 feet wide at the base, and probably served as the inspiration for the other more famous pyramids of Giza.

As chief lector priest, Imhotep's duty was to recite from the holy books. Since these contained magical formulas and in the minds of the people possessed magical powers, he was regarded as a magician who could influence the destinies of the dead. Another important priestly duty was to assist in the extensive and precise ceremonials and preparations required for burial. The embalming process must have furnished the opportunity for the study of human anatomy, just as animal sacrifice contributed to the knowledge of animal anatomy and physiology.

As chief scribe, Imhotep was honored daily by the thousands of copyists and amanuenses throughout the land. As a sage, he was one of Egypt's most honored. Twenty-five hundred years after his death, his proverbs were still sung by the people.

Little is known of Imhotep's attainments in astronomy. It is fair to assume that one so accomplished was familiar with the remarkably advanced concepts of that day, including a three-hundred-and-

sixty-five-day calendar, which had been adopted over a thousand years before his birth. The line between astronomy and astrology was not sharply drawn, and in the minds of the people his stature as a necromancer may have overshadowed his accomplishments as a scientist.

As a physician, Imhotep excelled. In fact, he so excelled that many of his "cures" must have been considered pure magic, which would account in some measure for his later deification. Study of the few medical papyri in existence today has given scholars some idea of what the practice of medicine was like five thousand years ago. The Edwin Smith Surgical Papyrus, translated by Breasted, is the most informative, for it not only is a copy of a book dating from the time of Imhotep but also may be a copy of a book written by Imhotep.[4]

In that papyrus is presented the first systematic study of disease known to history. Each process is presented as a list of symptoms, followed by a diagnosis. The manuscript, which is incomplete, begins with diseases of the head, and evidently an orderly progression through the rest of the body was made in the original. The disease is analyzed, and a statement whether treatment should or should not be attempted, according to the prognosis, is given. These ancient physicians made use of lint, bandages, sutures, adhesive materials, splints, casts, cauteries and drills. Some data indicate that actual dissection of the human body must have been made.

It was recognized unquestionably, says Breasted, that the heart was the center of the system for distributing the blood, though the actual circulation was not understood until the time of Harvey. The elementary significance of the pulse was appreciated as an indication of health and disease. The word "brain" was used for the first time in recorded speech, and paralysis of body after brain injury identified for these observers the localizing character of some brain injuries.

> Strange it is that the claims of Imhotep to be recognized as the titular deity of medicine have been so neglected. Many centuries before the exodus of the Israelites from Egypt (about 1230 B.C.), long before the recognition of Aesculapius by the Greeks as their legendary god of medicine, long before the days of Homer (about 850 B.C.), long before the birth of Hippocrates (about 460 B.C.), there lived in Egypt a magician-physician so famous for his skill in healing disease that he became recognized eventually as the god of medicine. . . . Tribute is due to a career so varied in its pursuits, so notable in its achievements, so trusted by suffering humanity, so glorified in its final deification.[2]

References

1. Breasted, J. H. *A History of Egypt: From the earliest times to the Persian conquest.* Second edition. 634 pp. New York: Scribner, 1912.
2. Budge, E. A. W. *The Rosetta Stone in the British Museum.* 325 pp. London: Religious Tract Society, 1929.
3. Hurry, J. B. *Imhotep, The Vizier and Physician of King Zoser and afterwards the Egyptian God of Medicine.* 118 pp. London: Oxford, 1926.
4. *The Edwin Smith Surgical Papyrus.* Translated by J. H. Breasted. 2 Vol. Chicago: University of Chicago Press, 1930.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

VIRGINIA W. TOWNE, *Assistant Editor*

BENJAMIN CASTLEMAN, M.D., *Editor*

CASE 41441

PRESENTATION OF CASE

First admission: A fifty-eight-year-old Russian-born building wrecker was admitted to the hospital for the first time because of recurrent chest pain.

Six years earlier he experienced a half-hour attack of squeezing chest pain. He was treated at an outside hospital, where an electrocardiogram was said to have been consistent with coronary thrombosis. Six months later a similar attack occurred, and he was treated at home by a private physician. After several months he returned to his heavy work. He now began to experience moderate exertional dyspnea and five-minute attacks of substernal squeezing pain radiating to the left elbow. These attacks occurred every few weeks, and were brought on by heavy exertion. They were relieved by rest and nitroglycerin. Two weeks before admission the episodes of pain became more frequent, occurring two or three times a day and necessitating stopping work. In the Out Patient Department an electrocardiogram was consistent with an old anterior myocardial infarct.

The past history was noncontributory.

Physical examination revealed a short, stocky, moderately obese man. There were no significant abnormal physical findings. The heart sounds were of fair quality, and the heart was not enlarged.

The temperature was 97°F., the pulse 76, and the respirations 20. The blood pressure was 110 systolic, 80 diastolic.

Urinalysis was negative except for the presence of 1 to 5 red cells per high-power field in the sediment. Examination of the blood revealed a hemoglobin of 14 gm. per 100 cc. and a white-cell count of 10,600, with 58 per cent neutrophils, 32 per cent lympho-

cytes, 6 per cent monocytes and 4 per cent eosinophils. The corrected sedimentation rate was 0.45 mm. per minute. An x-ray film of the chest was not remarkable. Serial electrocardiograms showed changes interpreted as being consistent with evolution of a recent anterior myocardial infarct.

Treatment consisted of quinidine and bed rest, and the patient was discharged asymptomatic in three weeks.

Second admission (two years later). During the interval since the first admission the dyspnea and intermittent pain in the chest had continued. Two months before admission he had a four-hour attack of pain in the chest and dyspnea. Since then, the exertional dyspnea was worse, and he began to have paroxysmal nocturnal dyspnea. Early in the morning before admission he was awakened by a feeling of substernal heaviness radiating to both shoulders and the left arm and associated with severe dyspnea. Later in the morning a local physician gave him morphine sulfate and prescribed bed rest. He reawakened dyspneic on the morning of admission and entered the Emergency Ward in acute pulmonary edema. Serial electrocardiograms gave evidence of an old anterior myocardial infarct and questionable evidence of a recent posterior infarct. He received the usual therapy along with Dicumarol and was discharged improved after three weeks.

Third admission (twenty-two months later) because of an attack of severe substernal pain radiating to the left scapula and left arm and accompanied by dyspnea. During the interval since the previous admission he had been taking digitalis and diuretics and had been placed on a low-sodium diet. The angina with only mild exertion persisted, and orthopnea relieved by two pillows developed. On physical examination the heart was enlarged to the anterior axillary line, and there was a Grade 2 apical systolic murmur. The liver edge was 2 fingerbreadths below the costal margin. The neck veins were distended when the patient was raised to 30°. The sedimentation rate and white-cell count were normal. Serial electrocardiograms were not significantly changed from those taken two years previously, although there were large P waves consistent with atrial hypertrophy. He again was treated with a cardiac regimen including Dicumarol and was discharged in two weeks.

Fourth admission (sixteen months later) because of increasing frequency and duration of attacks of substernal pain. Since the last admission he had daily anginal attacks, which were promptly relieved by nitroglycerin, of which he took 5 or 6 tablets a day. One month before admission he began having more or less continuous substernal pain, which was only partially relieved by 7 to 10 nitroglycerin tablets daily. Physical examination showed slight enlargement of the heart, distant heart sounds, scattered inspiratory and expiratory pulmonary rales and a slightly enlarged, nontender liver. Electrocardiograms showed no significant change from the previous tracings. Radioactive iodine, 29.8 millicuries, was administered. The pretreatment radioactive-iodine uptake was 28.5 per cent in twenty-four hours, and the protein-bound iodine was 5.7 microgm. per 100 cc.

Final admission (eleven months later at the age of sixty-four) because of increased dyspnea, fatigue, dizziness and almost constant chest pain over a period of two weeks. During the interval since the last admission the angina had improved whereas exertional dyspnea had greatly increased in severity. He continued taking digitalis, diuretics, nitroglycerin (0 to 6 tablets per day) and a low-salt diet. The protein-bound iodine three months after the radioactive-iodine treatment was 4.6 microgm. per 100 cc. Six months later he appeared clinically myxedematous, and the protein-bound iodine was 1.1 microgm. per 100 cc. He was started on 15 mg. of desiccated thyroid daily, two weeks before this last admission. Four days before admission a local physician removed some fluid from the right pleural cavity.

FIGURE 1.

Physical examination revealed a chronically ill, acutely dyspneic, sallow man. The eyelids were puffy, and the voice hoarse. The neck veins were distended 8 cm. above the clavicle when the patient was raised to 45°. The thyroid gland was not palpable. Both lung bases were dull to percussion, and there were numerous sticky rales scattered over the chest, as well as diffuse inspiratory and expiratory wheezes. The heart was enlarged 2 or 3 cm. to the right of the sternum and almost to the left anterior axillary line in the fifth intercostal space. The rhythm was regular. A soft systolic murmur and questionable diastolic gallop were heard at the apex. There was a 10-mm. pulsus paradoxicus. The liver edge was 6 cm. below the right costal margin and was slightly tender. There was a questionable fluid wave in the abdomen. Sacral edema was present, but there was no ankle edema.

The temperature was 99°F., the pulse 84, and the respirations 24. The blood pressure was 108 systolic, 86 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 14 gm. per 100 cc. and a white-cell count of 6000, with a normal differential. The sedimentation rate was 20 mm. in one hour. The cholesterol was 338 mg., the nonprotein nitrogen 30 mg., the total protein 6.6 gm., the albumin 4.0 gm., and the globulin 2.6 gm. per 100 cc. The venous pressure was equivalent to 220 mm. of water. Measurement of the circulation time gave no end point. An x-ray film of the chest showed a huge globular heart (Fig. 1). Old films were reviewed, and it was

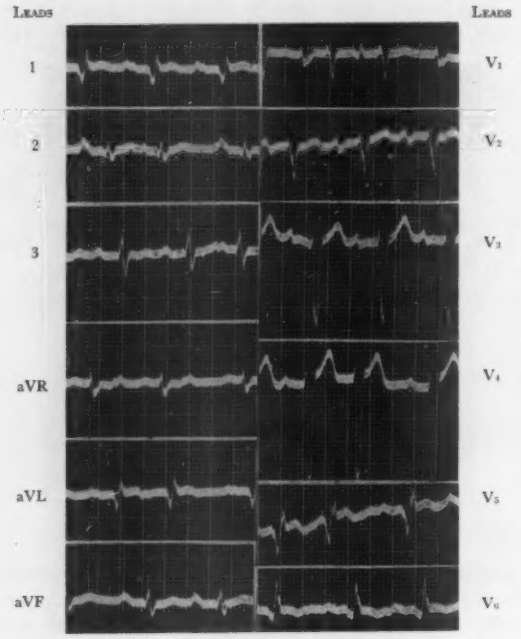


Figure 2.

believed that during the previous six years there had been no change in the shape of the heart, but that all chambers and diameters had enlarged. There was pulmonary vascular engorgement and fluid at the right costophrenic angle. An electrocardiogram gave evidence of old anterior and posterior myocardial infarctions and a nonspecific decrease in voltage since the previous tracing (Fig. 2). The patient's cardiac regimen was continued, and the dosage of thyroid was increased to 20 mg. daily. However, dyspnea increased, and he complained of more oppressive chest pain, which was relieved only by Demerol. He was found dead in bed on the fourteenth hospital day.

Differential Diagnosis

Dr. A. Stone Freedberg*: In summary this patient had suffered over a twelve-year period multiple episodes of prolonged cardiac pain, several of which were associated with electrocardiographic evidence of myocardial infarction, in addition to severe angina pectoris and congestive heart failure. The clinical phenomena represent an extreme discrepancy between the coronary supply and the myocardial demand, and indicate an inadequate development of coronary collateral circulation in response to what was probably the pathologic substrate of the symptoms — namely, severe coronary arteriosclerosis. Whether there were multiple coronary occlusions or just severe coronary narrowing, only the pathologist can tell us. It is probable that several of the episodes represented sudden narrowing related to hemorrhage within plaques or to acute coronary thrombosis. However, it must be remembered that approximately 50 per cent of the cases of acute myocardial infarction studied carefully by the Schlesinger technic[1,2] of dissection and injection and multiple sections do not show an acute fresh occlusion. The assumption that the pathologic process is coronary arteriosclerosis is based not only on statistical probabilities but also on the absence of evidence of other processes that we know to be associated with this kind of clinical course — namely, hypertension, valvular heart disease, including syphilis, and the rarer forms of coronary-artery disease such as thromboangiitis obliterans, periarteritis, scleroderma and amyloidosis.

There were two unusual features in the clinical course: the normal sedimentation rate and the large P waves. I do not think I can explain either one. There was no evidence of liver disease or of a blood abnormality that might have been responsible for the relatively normal sedimentation rate. We are not told what the hematocrit or hemoglobin was, but the blood globulins were normal. About the P waves, it is known that cardiac hypertrophy occurs with coronary arteriosclerosis and that this hypertrophy is increased when congestive heart failure takes place. The possibility that this man had coronary-artery disease resulting in an ischemic process involving the atria must be raised, but I know of no way to predict its occurrence clinically. There was no evidence that the tall P waves were related to atrial infarction and nothing to substantiate the conclusion that they were related to mitral valvular disease, pulmonary emboli or to the rare ball-valve thrombus or tumor of the left atrium.

Several questions, I think, can be raised about the final admission. No evidence of any of the unusual complications of myocardial infarction such as rupture of a septum, of a papillary muscle or of a chorda tendineae, or the development of mural ventricular thrombi is presented. Whether the final episode was related to a new coronary episode, to ventricular arrhythmia, or to the occurrence of pulmonary emboli, cannot be stated with any degree of certainty. No evidence was given to suggest that an aortic dissection had occurred.

*Visiting physician and associate director of medical research, Beth Israel Hospital.

The possibility has to be raised that the final episode was related to the myxedema induced in this patient by the radioactive iodine. The radiation delivered by the 30 millicuries if the radioactive iodine had a normal half life, within a normal-sized thyroid gland of approximately 25 gm., can be estimated to have been approximately 40,000 R.E.P. (Roentgen Equivalent Physical). It is of interest that about 8,000 R.E.P. is the average amount required to treat effectively hyperthyroidism; approximately 15 per cent of hyperthyroid patients became hypothyroid on this dose. The development of hypothyroidism was relatively slow in this man since three months after I^{131} the serum protein-bound iodine was 4.6 microgm. (normal, 4 to 8 microgm.). However, six months later (nine months after I^{131}) it was 1.1 microgm. per 100 cc. The patient had the characteristic clinical signs of myxedema — puffy eyelids, hoarse voice and the characteristic dizziness and fatigue that many patients with myxedema present. The slow circulation time is characteristic. The absence of a detectable end point in the circulation test can be attributed to the amount of material that was injected, with some tailing out of the infused material and therefore no taste. The x-ray findings of a large heart, the suggestion of the pericardial effusion, supported by the detection of pulsus paradoxicus, the low voltage in the electrocardiogram, and the serum protein-bound iodine of 1.1 microgm. per 100 cc. all confirm the presence of myxedema. It is interesting how little pericardial effusion will produce a pulsus paradoxicus. Only last week we saw a patient in the Beth Israel Hospital with pulsus paradoxicus who at autopsy had a pericardial effusion of only 150 cc. The existence of pericardial, pleural or ascitic effusion is well known in myxedema but rare enough to be reported. Time does not permit a discussion of the question whether the circulatory effects of myxedema are related to a direct cardiac effect, to pericardial effusion or to both. Are there distinguishing characteristics on x-ray examination?

Dr. Joseph Hanelin: Characteristically, the myxedema heart is increased in size and of configuration most closely resembling massive pericardial fluid accumulation; cardiac pulsations are diminished. This is in good part probably due to actual fluid within the pericardial sac, which has been demonstrated to be present in most cases. The lung fields may show a fair degree of congestive heart failure.

Dr. Freedberg: Sudden death has also been reported in myxedema. The cause of the sudden death in many cases has not been defined. The only pathologic finding has been hydropic degeneration of muscle cells. However, Kountz[3] reported 3 cases of myxedema with sudden death in which there was rupture of the aorta, the substrate being medionecrosis cystica. That that is unusual, I think, is attested by many studies starting with the initial study in the 1880's by the English,[4] who examined a large series of patients with myxedema.

Whether myxedema can produce congestive heart failure has been the subject of discussion for thirty years. It is striking that in the cases reported no clear evidence of congestive heart failure is present. Means, White and Krantz[5] and Lerman and others[6] from this hospital came to the conclusion that myxedema as a condition precipitating congestive heart failure or angina pectoris is very rare. There are also papers by Willius and Haines,[7] Christian[8] and others in support of this conclusion. Our experience[9] in perhaps 120 patients with myxedema induced by radioactive iodine and in 100 patients with myxedema induced by total thyroidectomy supports the conclusion that if the condition occurs, it occurs only rarely.

I should, therefore, interpret this patient's final episode of progressive congestive heart failure, venous distention, rales in the lungs and enlarged liver as being related to congestive heart failure produced by the severe coronary-artery disease and marked myocardial fibrosis, which he undoubtedly had.

To turn briefly to a discussion of the suitability of radioactive-iodine induction of hypothyroidism to treat intractable angina pectoris or congestive heart failure, there are three bases for our belief that the induction of myxedema might be helpful in euthyroid cardiac patients with intractable angina pectoris or congestive heart failure. One is the vast clinical evidence that the treatment of hyperthyroidism in patients with angina pectoris and congestive heart failure results in significant improvement or even disappearance of the symptoms of angina pectoris or congestive heart failure when the hyperthyroidism has been adequately treated. Moreover, in cases in which there is only partial improvement, the subsequent development of myxedema in such patients either spontaneously or in relation to therapy is associated with further improvement. Secondly, it is well known that bed rest, which decreases the demand on the myocardium, improves patients with angina pectoris or congestive heart failure. Hypothyroidism or myxedema is a condition in which the demands of the body on the heart are reduced because the body demands for oxygen are reduced in the presence of hypothyroidism. There is physiologic confirmation of this based on the experiments of Blumgart[10] in which he showed that patients with myxedema have a decreased velocity of blood flow and decreased cardiac output; nevertheless, they give no manifestations of congestive heart failure. Thirdly, the therapeutic results of I^{131} in a large series of 835 cases of severe angina pectoris treated in this country and abroad with radioactive iodine showed that approximately two thirds had an excellent or a good response and that one third did not.[11]

We would not conclude that the patient discussed here today had a good result. It is likely that the improvement in the angina pectoris was associated with the increasing severity of the congestive heart failure and decreasing exercise tolerance. The results of I^{131} in congestive heart failure are not quite as

good as those in angina pectoris. Only approximately 50 per cent of 400 patients with intractable congestive heart failure have had an excellent to good result with radioactive iodine; the remainder have not benefited. The mechanism of the therapeutic effect of I^{131}-induced hypothyroidism is not completely worked out and time prohibits my discussing it. I shall simply conclude by saying that it is possible that the mechanism of the beneficial effect is not the same in angina pectoris as in congestive heart failure.

DR. AUSTIN L. VICKERY: Dr. Maloof, do you have remarks about this patient?

DR. FARAHE MALOOF: It appears from this patient's record that the myxedema, which obviously developed, was bad for his heart. In general, I believe that complete athyreosis is bad for such patients and is bad for any patient. He was not seen from six months after the administration of radioactive iodine, when he was myxedematous, to eleven months after treatment, when he was in trouble. At this time thyroid was given for the first time.

DR. VICKERY: I think there was quite an interval when he did not return to the clinic.

DR. MALOOF: We have seen 3 or 4 similar patients who got into trouble and died after the development of myxedema. Hence, it is extremely important that such I^{131}-treated patients be followed closely by those who are acquainted with the over-all problem. Application of the indexes of thyroid function as the tracer and the serum protein-bound iodine may herald the development of myxedema several months before it is manifest clinically. The basal metabolic rate may be unreliable or may be difficult to determine in some cardiac patients. I should like to ask Dr. Freedberg about the long-term follow-up study of these euthyroid cardiac patients who have been treated with I^{131}.

DR. FREEDBERG: I cannot draw the conclusion that myxedema was bad for this patient's heart. Dr. Maloof would certainly agree that it is very difficult if not impossible to conclude that the cause of the final result in this patient was the myxedema. From the study of large numbers of cases, we are unable to conclude that myxedema is bad for the heart — that is, that a downhill course follows the induction of myxedema in the type of patient that we are treating. We can present cardiac patients with intractable angina pectoris who have had untreated myxedema because they refused to take thyroid or because we wanted to be sure all thyroid tissue had been destroyed. They have demonstrated all the manifestations of severe myxedema and yet have been markedly improved without clinical evidence of congestive heart failure and without angina pectoris. The experience cited above is confirmatory.

About the long-term follow-up study, we have been treating patients with radioactive iodine for over seven years. The longest follow-up period in our series is over seven years, and the average is approximately three years from the time of the onset of the myxedema. This is accurately predicted in our hospital because we see all the patients at frequent intervals (approximately three to six weeks) until hypothyroidism ensues, at which time we start the administration of desiccated thyroid in a daily dosage of 6 to 15 mg.

CLINICAL DIAGNOSES

Coronary-artery disease with ?recent myocardial infarction.
Congestive heart failure.
Myxedema, with pericardial effusion.

DR. A. STONE FREEDBERG'S DIAGNOSES

Severe coronary arteriosclerosis, with old myocardial infarction(s), myocardial fibrosis and heart failure.
Myxedema, induced by radioactive iodine.

ANATOMICAL DIAGNOSES

Coronary arteriosclerosis, severe, with myocardial infarction and aneurysmal dilatation.
Fibrosis of thyroid gland, marked (after radioactive iodine).
(Myxedema heart disease).
Pulmonary congestion and edema.
Hydrothorax.
Pericardial effusion, slight.
Chronic passive congestion of liver, severe.

PATHOLOGICAL DISCUSSION

DR. VICKERY: At autopsy, the heart was considerably enlarged, weighing 650 gm.; all chambers were dilated, giving the organ a globular configuration, and the myocardium had a flabby consistence. There was marked thinning with fibrosis representing old infarction involving the left ventricular apex that extended up into the left ventricular wall and septum. There was no valvular disease. The coronary arteries displayed a severe degree of atherosclerosis; however, no site of recent occlusion was identified, which, as Dr. Freedberg remarked, is not infrequent in this type of patient. An additional important finding was that of a pericardial effusion, which, although of only 100 cc., was probably consistent with myxedema.

The thyroid gland showed marked scarring and weighed only 8 gm. Microscopically, the effects of the I^{131} therapy were indicated by diffuse radiation fibrosis and only scattered residual thyroid follicles. Other pertinent autopsy findings included a right-sided pleural effusion (300 cc.) and severe pulmonary congestion and edema.

In addition to the coronary-artery disease, we considered the cardiac findings in this case consistent with the diagnosis of myxedema heart disease. Since there are no known pathologic features that are specifically diagnostic of this entity,[12] it is perhaps better to consider myxedema heart disease as a clinicopath-

ological syndrome. Although stating that the exact cause of the cardiac enlargement is not clear, Dr. Paul D. White[13] has referred to three possible factors contributing to the enlarged x-ray heart shadow associated with about three fourths of the cases of myxedema: dilatation, increased bulk of heart muscle (? due to interstitial edema) and pericardial effusion. In Gould's textbook, Wartman and Hill[12] refer to the excessive pericardial fluid often found in myxedematous patients and comment on the confusion in the literature regarding myocardial changes attributable to myxedema. Schnitzer and Gutmann,[14] in a study of pericardial effusion and myxedema, suggest that pericardial effusion may be the most common factor in myxedema heart disease and comment on the pericardial effusions and flabby hearts found in thyroidectomized sheep and goats. These authors further state that there is no positive histologic evidence proving the existence of a myxedematous alteration of myocardium. Microscopically, the myocardium of this patient did give some evidence of interstitial edema perhaps relatable to flabbiness, which, coupled with the marked cardiac dilatation and the pericardial effusion, form the basis of the diagnosis of myxedema heart disease. Furthermore, Dr. White[13] has stated that patients with severe coronary-artery disease, which this patient certainly had, are perhaps more prone to develop cardiac dilatation and weakness with a myxedema state.

The pituitary gland weighed 600 mg., which is about 30 per cent above the average weight. Dr. Agnes Burt Russfield, from our laboratory, has shown in a series of myxedematous patients that an enlarged pituitary gland is a fairly constant finding and that it is attributable to what is interpreted as an increase in the amphophil cells, which are thought to be the source of thyroid-stimulating hormone.

DR. FREEDBERG: Was there evidence of injury to the parathyroid glands?

DR. VICKERY: No.

DR. EARLE M. CHAPMAN: Was there any evidence of cancer in the thyroid gland?

DR. VICKERY: No; there was not.

REFERENCES

1. Schlesinger, M. J. Injection plus dissection study of coronary artery occlusions and anastomoses. *Am. Heart J.* **15**:528-568, 1938.
2. Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M. Angina pectoris, coronary failure and acute myocardial infarction: role of coronary occlusions and collateral circulation. *J.A.M.A.* **116**:91-97, 1941.
3. Kountz, W. B. Vascular degeneration in hypothyroidism. *Arch. Path.* **50**:765-767, 1950.
4. Report of committee of Clinical Society of London to investigate subject of myxedema. *Transactions of the Clinical Society of London.* Vol. 21 (Supplement). Longman Green, 1888.
5. Means, J. H., White, P. D., and Krantz, C. I. Heart in myxedema, with special reference to dilatation and angina pectoris. *Boston M. & S. J.* **195**:455-460, 1926.
6. Lerman, J., Clark, R. J., and Means, J. H. Heart in myxedema: electrocardiograms and roentgen-ray measurements before and after therapy. *Ann. Int. Med.* **6**:1251-1271, 1933.
7. Willius, F. A., and Haines, S. F. Status of heart in myxedema. *Am. Heart J.* **1**:67-72, 1925.
8. Christian, H. A. Myocardial disturbances due to abnormal thyroid function and their management. *Pennsylvania M. J.* **32**:70-74, 1928.
9. Kurland, G. S., Schneckloth, R. E., and Freedberg, A. S. Heart in I^{131}-induced myxedema. *New Eng. J. Med.* **249**:215-222, 1953.
10. Blumgart, H. L. Velocity of blood flow in health and disease: velocity of blood flow in man and its relation to other measurements of circulation. *Medicine* **10**:1-75, 1931.
11. Blumgart, H. L., Freedberg, A. S., and Kurland, G. S. Treatment of incapacitated euthyroid cardiac patients with radioactive iodine: summary of results in treatment of 1,070 patients with angina pectoris or congestive failure. *J.A.M.A.* **157**:1-4, 1955.
12. Wartman, W. B., and Hill, W. T. Degenerative diseases. In S. E. Gould. *Pathology of the Heart.* 1040 pp. Springfield: Thomas, 1953.
13. White, P. D. *Heart Disease.* Fourth edition. 1015 pp. New York: Macmillan, 1951. Pp. 453-458.
14. Schnitzer, R., and Gutmann, D. Myxoedema with pericardial effusion. *Brit. Heart J.* **8**:25-28, 1946.

CASE 41442

PRESENTATION OF CASE

A fifty-four-year-old paint-factory worker entered the hospital for the first time because of black stools.

Fourteen years before admission he had indigestion and black stools, for which he was hospitalized and

FIGURE 1. *Lateral View of the Distal Esophagus and Stomach, Showing Partial Obstruction of the Lower Esophagus and Irregularity of the Gastric Fundus.*

given blood transfusions. A posterior gastroenterostomy was performed after a diagnosis of peptic ulcer was made. He was well subsequently, until two years before admission, when he noted a few black stools. An x-ray film showed a large stomal ulcer. He was treated with diet and was able to keep on working until six weeks before admission, when he became weak and had pain in the right side of the abdomen. A gastrointestinal series at that time revealed a scarred duodenal cap, and the radiologist suggested the possibility of a hepatic tumor invading the stomach. He stopped working and was treated with liver extract. Since then, he had lost 20 pounds and noted a gradual increase in abdominal girth. On the day of admission he again had black stools and came to the Emergency Ward because he knew the seriousness of this symptom.

He had been a heavy drinker for years until two years previously. There was no history of previous jaundice.

Physical examination revealed a jaundiced and emaciated man with a large protuberant abdomen.

Prominent dilated veins were present over the upper abdomen and chest, and spider angiomas were also observed over the abdomen and chest. The lungs and heart were normal on auscultation and percussion. The breasts showed an increase in glandular consistence. The liver was firm; its edge was palpable 3 fingerbreadths below the costal margin and was somewhat irregular. Shifting dullness was detected in the abdomen. The spleen was not palpable. Rectal examination was negative. The testes were small; there was ++ pretibial edema.

The temperature was 96.4°F., the pulse 120, and the respirations 36. The blood pressure was 100 systolic, 60 diastolic.

Urinalysis showed + tests for albumin and diacetic acid, a +++ test for bile and 3 to 5 white cells and 2 to 3 red cells per high-power field in the sediment. Examination of the blood revealed a hemoglobin of 4.0 gm. per 100 cc. and a white-cell count of 35,000, with 90 per cent neutrophils. The bilirubin was 4.5 mg., the alkaline phosphatase 1.4 units, and the nonprotein nitrogen 50 mg. per 100 cc. The stool gave a ++++ guaiac test. Gastric contents were "coffee grounds."

An x-ray examination of the upper gastrointestinal tract was not ideal because the patient could not stand. The esophagus appeared dilated, and barium flowed into the stomach with difficulty; however, the distal esophagus was smooth in outline (Fig. 1). There was inadequate filling of the fundus, and there appeared to be two ulcers in this region. A filling defect was seen in the body of the stomach. Ascites was present. The x-ray film of the chest showed high leaves of the diaphragm and an increase in hilar densities. The heart was not enlarged.

The patient received 6 units of blood, after which the hemoglobin rose to 9.5 gm. per 100 cc. At paracentesis 4000 cc. of dark, bloody fluid was removed. Overnight the hemoglobin dropped from 9.0 to 5.9 gm. per 100 cc. He was re-examined, and the findings were similar to the previous ones, but this examiner felt a questionable nodule in the abdominal wall below the umbilicus and noted no spider angiomas and only questionable scleral icterus. Many superficial venous thromboses were found, however. A diagnostic paracentesis was done; only a few cubic centimeters of grossly bloody fluid, whose hemoglobin content was 5.3 gm. (the peripheral blood hemoglobin was 5.9 gm.) was removed. He was further transfused to a total of 5500 cc., but his blood pressure dropped steadily during the day, and he was found dead in bed early the next morning, thirty-six hours after admission.

Differential Diagnosis

Dr. Warren Point*: The protocol and past history offer abundant evidence that this patient had cirrhosis of the liver: jaundice, hepatomegaly, gynecomastia, testicular atrophy, ascites, spider angiomas, dilated collateral veins, irregular liver edge and finally a good etiologic background of heavy alcoholism. It is interesting that an occupational exposure to paint seems to be associated with alcoholism so often.

Six weeks before entry, the patient had right-sided abdominal pain, weakness and clinical signs of increasing liver decompensation. This course, in a patient with cirrhosis, together with the later discovery of bloody ascites, makes the diagnosis of hepatoma very likely. I am not daunted by the absence of a palpable spleen, for ascites may obscure this, nor by the absence of demonstrable varices, since the x-ray examination was by no means satisfactory. The low alkaline phosphatase is evidence against carcinomatous involvement of the liver, but it was so low as to be almost inconceivable, so that I shall disregard this finding altogether. We know that he had chemical jaundice so that the second observer's doubt concerning scleral icterus is not a valid observation. There is no other information given concerning liver-function tests, but I see no real need for any more; it would be nice to know the cephalin flocculation, serum albumin and prothrombin. I shall therefore offer a definite diagnosis of cirrhosis of the liver, with possibly hepatoma superimposed.

I do not see how I can tie the cirrhosis and the x-ray findings together. Dr. Hanelin, will you show us what the radiologist found?

Dr. Joseph Hanelin: Proper study of the intestinal tract radiographically includes both careful fluoroscopy and filming, and in this particular case, without the benefit of the fluoroscopic observation, it is extremely difficult to make any positive statements concerning the abnormality described at the esophagogastric junction and in the stomach itself. There is, however, indication of partial obstruction of the distal esophagus, slightly above the level of the diaphragm (Fig. 1). The fluoroscopist thought that the esophagus was fairly smooth in this region, and although it is irregular in a number of films, this is not a consistent finding. The constricted area itself is relatively short, not more than 2 cm., and below it there is probably a hiatus hernia with two areas of barium pooling within it, which were thought to represent ulcerations. There is irregularity of the fundus of the stomach below the level of the suspected hiatus hernia, and a number of defects are made out elsewhere within the gastric lumen, which may or may not be significant. They could represent retained débris. In the abdominal films, no barium is noted to have left the stomach through the pylorus. There is, however, an accumulation of barium in what may be the distal loop at the stoma. For some reason, barium has not progressed for more than 5 cm. from the site of the gastroenterostomy. Marked ascites is evident, largely obscuring details of the visceral structures. There is a sausage-shaped density lying in the left side of the abdomen that could represent a distended loop of

*Assistant in medicine, Massachusetts General Hospital.

small bowel. The lungs are clear, although there is minimal atelectasis at the bases secondary to the elevated diaphragm. No varices are seen in the esophagus, but these could easily be obscured by the excessive barium retention.

DR. POINT: In addition to an incomplete history, probably because the patient was too sick, we are presented with an unsatisfactory x-ray examination of the upper gastrointestinal tract. Something held up the progress of barium through the cardia, and I do not believe it was the varices that we do not see. Just below this we see two probable ulcers, and this was not surprising in a patient with such a strong past history of ulcer. Often, localization of ulcers in the cardia is due to a hiatus hernia and peptic-ulcer formation in the herniated portion of the stomach. Of course, this ragged area could be cancer. The negative past history is surprising, but in a patient with recurrent ulcers, symptoms of hiatus hernia might be overlooked quite easily. One point favoring cancer of the cardia is the apparent filling defect, which seems to divide the upper stomach into two columns. This point is not at all clear to the radiologist, and I shall not give it much diagnostic significance. The dividing "lump" may be an artifact. I wonder, too, if this is not the area that the first radiologist believed was hepatic tumor invading the stomach.

We must also consider cancer of the pancreas invading the stomach wall, with subsequent malformation of the cardia, and superficial venous thromboses, a well recognized sign in cancer of the pancreas. I have no right to do other than mention this possibility, and I suspect that the pathologic area is a little high for any but cancer of the tail of the pancreas.

One other possibility in the cardia is leiomyosarcoma with ulceration and bleeding. This is statistically much rarer than carcinoma or hiatus hernia with ulcers, so I shall only mention it.

Whatever the etiology of the lesion in the cardia, it would seem sufficient to account for tarry stools and anemia. I must admit also that the gradual development of anemia due to oozing of blood from the stomach may have been the cause of hepatic decompensation — in which case my diagnosis of hepatoma becomes less necessary to explain the picture. If the hemoglobin on entry was only 4.0 gm. per 100 cc., I am certain that he had been anemic for some time. The blood pressure on admission was 100 systolic, 60 diastolic, but a profound shocklike state was not described.

A disturbing feature is the white-cell count of 35,000, with 90 per cent neutrophils. This is a little high for the leukocytosis of blood loss, or even the toxic effect of hepatic-cell necrosis. I do not believe it is out of line with a necrotic hepatoma. There is no mention of the temperature after the initial low reading, and I do not know how well the white-cell count and the temperature jibe. The figure of 35,000 is quite in keeping with thrombosis of the bowel, either venous or arterial. We have already heard that superficial venous thromboses were observed. These are considered to be more characteristic of pancreatic cancer than deep venous thromboses are, but it is an interesting thought. This suspicion is reinforced by the x-ray demonstration of a loop of questionably distended small bowel in the left flank, even though it is not gas filled. Infarcted small bowel can account for blood in stools, but I do not believe it had been present long enough to produce the profound anemia that this patient had. I shall assume that "coffee-grounds" gastric contents represented blood; this is probably not accounted for by the diagnosis of small-bowel infarct. It is possible that portal-vein thrombosis with secondary venous infarction of the bowel had occurred, and this is reasonable enough to mention as a by-product of the cirrhosis and questionable hepatoma.

The terminal episode is not clear. It is obvious that the patient died of shock secondary to hemorrhage, but the site of bleeding is not known. It may have been directly into the gastrointestinal tract from esophageal varices or from the stomach lesion itself, or may have been into the peritoneal cavity — a fact that is suggested by the grossly bloody paracentesis. I shall disregard this differential point since I believe that a needle properly placed in the peritoneal cavity of this patient would have yielded more than a "few cubic centimeters" of bloody fluid. It was more probably a traumatic bloody tap. I expect that the bowel was filled with gross blood at autopsy.

I cannot explain the nodule in the abdominal wall except to say that it may have been tumor. Hepatoma is an unlikely source, and I suppose cancer of the stomach is the best bet here. I have made no mention of metastatic cancer to the liver from pancreas, stomach and so forth. This diagnosis seems unnecessary, and metastatic cancer is much less likely to produce bloody peritoneal fluid than either hepatoma or infarcted small bowel.

I am also concerned about the holdup in the gastroenterostomy stoma. Whether this occurred because not enough barium entered the stomach, or because of some stomal lesion, I do not know. A stomal ulcer must be considered as a source of blood loss and partial obstruction. We have so little evidence for discussion of disease in this area that I shall only mention the possibility. Lack of knowledge of the prothrombin time prevents me from ruling out low prothrombin as a cause of bleeding, but I doubt it.

In conclusion, I believe this patient had Laënnec's cirrhosis of the liver, with progressive necrosis and probable hepatoma. There is a strong possibility of portal-vein thrombosis and bowel infarction. In addition, he had a separate lesion of the cardia, which I

shall call a hiatus hernia, with two peptic ulcerations and massive gastrointestinal hemorrhage from that.

DR. ROBB H. RUTLEDGE: When the patient entered the Emergency Ward because of gastrointestinal bleeding, it was believed that the bleeding was not severe enough to account for the anemia and debilitation. Consequently, we were worried about an underlying malignant neoplasm, probably carcinomatosis because of the distended abdomen. The gastrointestinal series was inconclusive; therefore, we did the paracentesis, which we believed established the diagnosis of carcinomatosis. We did not know the source, but thought that the stomach was the most likely, with pancreas second and liver third.

CLINICAL DIAGNOSES

Intra-abdominal carcinoma, probably gastric in origin.
Gastrointestinal bleeding.
Intra-abdominal bleeding.
Posterior gastroenterostomy.
Probably nutritional liver disease.

DR. WARREN POINT'S DIAGNOSES

Laënnec's cirrhosis of liver.
Hepatoma.
Thromboses of portal vein.
Hiatus hernia, with peptic ulcerations of cardia.

ANATOMICAL DIAGNOSES

Hepatoma, with metastases to peritoneum and lungs.
Portal cirrhosis, alcoholic type, inactive.
Hemoperitoneum (1000 cc.) within greater omental sac.
Tumor thromboses of portal and hepatic veins.
Ascites (500 cc.).
Esophageal and paraesophageal varices.
Fibrocongestive splenomegaly (900 gm.).
Pulmonary edema and congestion, moderate.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: At autopsy the peritoneal cavity contained about 5 liters of bloody fluid, and, as Dr. Point predicted, the liver was the organ of particular interest. It weighed 3100 gm. — about twice the normal weight — and was almost completely replaced by many irregular-sized nodules of yellow-brown and yellow-green tumor tissue. Most of the nodules were necrotic, and this change probably accounted for the leukocytosis, as Dr. Point suggested. Tumor had extended into the smaller radicles of the hepatic vein and for a distance of 3 cm. in the portal vein, which it had occluded. There were also metastases to the peritoneum and diaphragm and to the greater omentum. Between the leaves of the omentum was about a liter of blood clot, which apparently had its origin in the necrotic tumor present in the omentum. This mass probably accounted for the obstruction to the flow of barium from the stomach noted on x-ray examination.

Although on gross examination of the liver there was so much tumor that it was difficult to evaluate the status of the remaining hepatic parenchyma, microscopical sections revealed that the normal architecture was altered by the presence of fibrosis and nodules of fairly uniform size, typical of a Laënnec cirrhosis. The cirrhotic process was inactive, and there was no recent liver-cell necrosis. The tumor was made up of large and small masses of cells closely resembling hepatic cells in uniformity, size and staining qualities, and often they were arranged in cords. An additional observation indicating the degree of differentiation of the tumor was the presence of bile stasis in the tumor cells not very different in form from that seen in nearby normal liver parenchyma.

There were many large varicose veins in the omentum and peritoneal surfaces reflecting the portal hypertension. Similarly, the spleen demonstrated the changes of congestive splenomegaly and weighed 900 gm. In the esophagus there were numerous large varices, but the mucosa appeared to be intact. The stomach was distended with white barium, and no mucosal lesions of any kind were discovered in either the stomach or the duodenum. The small bowel was congested to the point of being dusky red and contained blood-stained material, both apparently the result of the back pressure resulting from the portal-vein thrombosis. In the absence of peptic ulcers or erosion of esophageal varices it seems likely that this was the source of the patient's tarry stools.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

OWNED BY THE SOCIETY AND
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE
COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. — Richard E. Alt, M.D.
Oliver Cope, M.D. — James M. Faulkner, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. — Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Robert O'Leary, ASSISTANT EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
Henry R. Viets, M.D. — Benjamin Castleman, M.D.
Dwight O'Hara, M.D. — J. Englebert Dunphy, M.D.
Fletcher H. Colby, M.D. — Robert W. Buck, M.D.
Robert L. Goodale, M.D. — Herrman L. Blumgart, M.D.
Chester M. Jones, M.D. — Frank N. Allan, M.D.
Harvey R. Morrison, M.D. — Harvey A. Kelly, M.D.
Maxwell Finland, M.D. — Langdon Parsons, M.D.
Vernon P. Williams, M.D. — Mark Aisner, M.D.

MANUSCRIPTS, including references or bibliography, should be typewritten double spaced and submitted as original copy. References should conform to the style of the *Quarterly Cumulative Index Medicus* (listing name and initials of author, title of article, journal, volume number, first and last pages and year), and should be cited numerically in the order in which they appear in the text; the number should be limited to the absolute minimum.

ILLUSTRATIONS are reproduced as half tones and zinc etchings. Photographs must be distinct, and drawings done in black ink on white paper and each properly labeled.

MATERIAL printed in the *New England Journal of Medicine* is covered by copyright. Articles are accepted for consideration with the understanding that they are contributed for publication solely in this journal. The *Journal* does not hold itself responsible for statements made by any contributor.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

COPY for advertisements is accepted by the advertising committee of the *Journal* on the basis of the apparent quality and usefulness of the product and the manner of its presentation. Proprietary names of pharmaceutical products must be accompanied by the chemical, or generic or official names, and the quantity of all active substances and the recommended dose must be stated. Copy should be factual, conservative and in good taste.

ALTHOUGH it is believed that all advertising material accepted conforms to ethical medical standards, acceptance does not imply endorsement by the *Journal*.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

ORAL ADMINISTRATION OF PENICILLIN

IN 1953 Brandl, Giovannini and Margreiter[1] produced a new form of penicillin — namely, phenoxymethylpenicillin, or penicillin V. The physical and chemical properties of penicillin V suggested that it might be more satisfactory than penicillin G for oral administration. Both the free acid and the potassium salt of the newer antibiotic were shown to be more stable at the acid pH of the stomach, at which penicillin G may be largely inactivated. Both in animals and in human subjects these authors demonstrated a clear superiority of penicillin V over penicillin G when given orally, as evidenced by higher peak levels in the blood and longer periods over which higher levels could be demonstrated. On the other hand, on intramuscular administration, the reverse appeared to be true because of more rapid elimination, adsorption or destruction of penicillin V in the body, as compared with penicillin G. Experiments on acute and chronic toxicity of penicillins V and G showed almost identical results. Because of these physical and chemical properties and the results of these absorption studies, the authors considered penicillin V to be a new agent eminently suitable for oral therapy and representing an advance in penicillin therapy.

In a subsequent study, Giovannini,[2] confirming the earlier findings of McDermott et al.,[3] showed that orally administered penicillin is absorbed primarily from the duodenum; from that site both penicillin G and penicillin V are rapidly absorbed, and both are poorly absorbed from lower intestinal segments. Earlier studies indicated that part of the loss of activity of penicillin G was due to gastric acidity, and this could be avoided by administration before a meal or together with a buffer,[4] which helped protect it to some extent until it reached the duodenum.

Attempts to improve the absorption of penicillin G were made by its combination with dibenzylethylenediamine in benzathine penicillin; observations with this form led several workers[5-9] to believe that it resulted in prolonged absorption and action. In no case, however, were these deductions based on controlled observations, or even on contemporaneous comparisons made by the same methods. On the contrary, in every study in which any valid comparisons were made between benzathine penicillin and a buffered sodium or potassium salt of penicillin G, when both were given orally, the latter proved to give higher and more prolonged blood levels and greater urinary recoveries.[10-15] Moreover, absorption of benzathine penicillin from oral administration proved more erratic, and the delayed absorption in some persons was found to be the feature that may have led to the erroneous deduction that blood levels were sustained longer. The direct comparisons showed that, by the higher peak levels and the more sustained levels in the blood and the greater proportion of the administered drug that was recovered in the

urine, buffered potassium penicillin G given by mouth yielded three to six times the amount of penicillin activity of orally administered benzathine penicillin.[10-15]

On the other hand, the recent results with penicillin V, as indicated from the reports cited above and from the observations presented by Jones and Finland in this issue of the *Journal*, show it to be definitely superior to penicillin G for oral use. This should mean a more efficient utilization of orally administered penicillin given as penicillin V and suggests that the value of oral penicillin may thus be extended. Penicillin V may therefore represent the first advance in oral penicillin therapy since the introduction of buffers to improve the absorption of penicillin G and the use of probenecid (Benemid), which maintains higher blood levels by inhibiting renal excretion of penicillin.[16]

These observations on oral administration do not imply any similar comparisons of the three forms of penicillin when they are used intramuscularly. The much prolonged absorption of intramuscularly administered benzathine penicillin is now well known and is of proved usefulness in diseases in which low penicillin levels, sustained for long periods, are useful, as in the treatment of syphilis or of hemolytic streptococcal pharyngitis, or in the prevention of streptococcal infections. Penicillin V is distinctly inferior to penicillin G for intramuscular administration, according to the observations of Giovannini.[2] Moreover, probenecid may be expected to have similar effects in increasing the blood levels from both penicillins V and G.

On the other hand, it may be expected that the conjugation of benzathine with penicillin V will detract from its usefulness in the same manner that it reduces the levels of penicillin G. Unless equally controlled experiments can show conclusively that penicillin V acts differently from penicillin G when combined as benzathine penicillin V, the conjugated preparation should be avoided for oral use. Nor is there reason, at this time, to assume that a benzathine penicillin V would be a useful substitute for benzathine penicillin G for intramuscular administration.

References

1. Brandl, E., Giovannini, M., and Margreiter, H. Untersuchungen über das säurestabile, oral wirksame Phenoxymethylpenicillin (Penicillin V). *Wien. med. Wchnschr.* **103**:602-607, 1953.
2. Giovannini, M. Vergleichende Untersuchungen von Penicillin G und Penicillin V nach oraler Verabreichung. *Wien. med. Wchnschr.* **104**:910, 1954.
3. McDermott, W., Bunn, P. A., Benoit, M., DuBois, R., and Reynolds, M. E. Absorption, excretion, and destruction of orally administered penicillin. *J. Clin. Investigation* **25**:190-210, 1946.
4. Cohlan, S. Q., Lewis, S. M., and Seligman, E. Blood levels of penicillin with oral use of buffered and unbuffered solutions: studies on series of infants and children. *Am. J. Dis. Child.* **75**:15-23, 1948.
5. Elias, W., Price, A. H., and Merrion, H. J. N, N' dibenzylethylenediamine penicillin: new repository form of penicillin. *Antibiotics & Chemother.* **1**:491-503, 1951.
6. Lepper, M. H., Rodrigues, J., Blatt, N., and Spies, H. W. Use of dibenzylethylenediamine penicillin administered orally in bacterial infections. *Antibiotics & Chemother.* **2**:175-178, 1952.
7. Corriell, L. L., McAllister, R. M., Preston, E., III, and Hunt, A. D. Scarlet fever and mixed infections of throat and nasopharynx treated orally with dibenzylethylenediamine dipenicillin G. *Antibiotics & Chemother.* **3**:357-367, 1953.
8. Cathie, J. A. B., and MacFarlane, J. C. W. Oral N, N' dibenzylethylenediamine penicillin in children. *Brit. M. J.* **1**:805, 1953.
9. Beasley, D. M. G., and MacPherson, M. J. Benzathine penicillin by mouth in children. *Lancet* **1**:861, 1954.
10. Foltz, E. L., and Schimmel, N. H. Comparison of orally administered penicillin. I. N, N' dibenzylethylenediamine dipenicillin G. II. Procaine penicillin. III. Potassium penicillin G. *Antibiotics & Chemother.* **3**:593-599, 1953.
11. Bayne, G. M., Gylfe, J., Carfagno, S., and Boger, W. P. Benzethacil (Bicillin): report on penicillinemia following its oral administration in man. *Am. J. M. Sc.* **225**:190-196, 1953.
12. Wright, S. S., Purcell, E. M., Kass, E. H., and Finland, M. Penicillin G and benzethacil by mouth: comparison of penicillin levels in plasma of normal men after single oral dose. *J. Lab. & Clin. Med.* **42**:417-429, 1953.
13. Budolfsen, Sv. E., Hansen, S. E. J., and Rud, E. Oral administration of penicillin: comparative study of benzathine penicillin, procaine penicillin and potassium penicillin. *Acta pharmacol. et toxicol.* **11**:49-54, 1955.
14. Boger, W. P., Strickland, S. C., and Gylfe, J. M. Penicillinate of benzylhydramine: its oral administration. *Antibiotic Med.* **1**:372-376, 1955.
15. Strickland, S. C., Gylfe, J. M., and Boger, W. P. Hydrabamine penicillin G: new oral penicillin. *Antibiotic Med.* **1**:388-393, 1955.
16. Boger, W. P., and Strickland, S. C. Probenecid (Benemid): its uses and side-effects in 2,502 patients. *Arch. Int. Med.* **95**:83-92, 1955.

RED FEATHER CAMPAIGN

With the 1955 drive of the United Community Services well under way, it seems worth while to examine the merits of this annual appeal for funds. The campaign represents a sensible effort to obtain support for the 277 health and welfare agencies serving the 48 cities and towns of Metropolitan Boston, without the burdensome individual demands for funds that, in the past, have made the fall of the year a curse to the citizenry. It is hoped that a generous response will reduce to a minimum the solicitations from other organizations.

This year's drive stresses support of services for childhood and youth, in the belief that babies and children will grow up into useful citizens if they are not overcome by indigence and handicaps, and that juvenile delinquency will be a less serious problem if projects such as the Boy and Girl Scouts, youth clubs and summer camps are encouraged. To this end, more than 60 per cent of the money raised in the Red Feather campaigns is allocated to aid for youth.

These services and others concerned with various aspects of the public welfare are an essential part of the life of the community and deserve generous support. It is hoped that the local goal of $6,400,000 will be attained.

POLIOMYELITIS VACCINE PROGRAM DEFERRED

The Technical Committee on Poliomyelitis Vaccine of the Massachusetts Department of Public Health late in September recommended that the Massachusetts vaccination program be deferred until studies now in progress clarify further the safety and effectiveness of the vaccine. This decision was immediately approved by the State Advisory Committee on the vaccine, which is responsible for controlling its distribution.

The Advisory Committee further recommended that the decision be publicized to all physicians with

the note, however, that vaccine approved by the National Institutes of Health is available through drugstores and may be administered with due observance of the priorities established by the Committee. These limit the use of the vaccine, until further notice, to those in ages five through nine.

The reasons for deferring the state-wide programs are that immunity for a considerable proportion of the susceptible population has been produced by the recent epidemic and that the next poliomyelitis season is nine months away, giving time for the collection and study of more data and for a calmer appraisal of the situation.

This action has been approved by the Massachusetts Chapter of the American Academy of Pediatrics, which stresses the sound assumption that another epidemic year is not likely in the near future in this area. The Chapter, in a letter to its members, calls attention also to the fact that vaccine still contains the virulent Mahoney strain of Type I virus and that the carefully supervised vaccine program in Canada has been suspended because of the recovery of live virus in the vaccine.

The annual report of the National Foundation for Infantile Paralysis has been submitted as the proud record of poliomyelitis-fighting activities during 1954. The report, however, is announced as stopping short of the news that heartened the world last April, that the preventive represented by the vaccine had proved safe, potent and effective.

T. DUCKETT JONES MEMORIAL FUND

Dr. Thomas Duckett Jones, who died last November at the age of fifty-five, had spent the most active years of his career, from 1928 to 1948, in Boston as director of the House of the Good Samaritan. An internationally recognized authority on rheumatic fever, he was, at the time of his death, president of the National Health Council, a member of the Advisory Council of the National Heart Institute and medical director of the Helen Hay Whitney Foundation in New York City.

In view of the score of productive years that he spent in Boston and his many contributions to the study of rheumatic fever, the friends of Dr. Jones in this area will be particularly interested in the memorial fund that is being established in his name. Not only are contributions to the T. Duckett Jones Memorial Fund solicited, but also suggestions regarding the administration of such a fund. The committee in charge is of the present opinion that research in rheumatic fever should be given priority by the administrators of the fund, but not an exclusive claim on its income. Fellowships for promising young investigators and short-term support to permit completion of studies or projects by investigators holding permanent positions are considered to be in line with Dr. Jones's own philosophy and professional interests. If sufficient funds are available the establishment of a T. Duckett Jones professorship in an appropriate field in a university to be selected may be considered.

Suggestions and contributions should be sent to the T. Duckett Jones Memorial Fund, 525 East 68th Street, New York 21, New York.

Dr. J. A. Wood's Spiral Spring Supporter will be found a useful adjunct in the treatment of lateral curvatures of the spine, affording support, and at the same time allowing motion in any direction.

Boston M. & S. J., *Nov. 8, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Pulmonary Atelectasis and Emphysema

A twenty-seven-year-old gravida IV, para III, died during cesarean section, thirteen days before her estimated date of confinement.

Scheduled for her fourth section, she received at 7:00 a.m. 0.2 gm. of Seconal by mouth. An hour later a single spinal injection was given consisting of 14 mg. of Pontocaine with 1 per cent dextrose to a volume of 2.1 cc. Immediately before the injection 2 mg. of Neo-Synephrine was given intramuscularly. The blood pressure remained constant at 124 systolic, 90 diastolic, the patient being conscious and rational.

Shortly afterward the operation was begun, and as the peritoneum was opened Trendelenburg position was requested. This position was instituted about 20 minutes after the anesthetic had been injected. Immediately, the patient became cyanotic and stopped breathing. The blood pressure and pulse disappeared. Her condition did not improve with the administration of oxygen, Methergine, 1 cc., or Nalline, 5 mg., becoming steadily worse despite oxygen given under positive pressure. A bladder flap was rapidly developed, and a living baby delivered with difficulty through a Kerr incision. After resuscitation the baby breathed, subsequently remaining well.

The surgeon states, "At the time of delivery of the infant, the patient was cyanotic, and it was believed that if the baby was delivered, at least the patient would have a chance to breathe better and also that the infant would be saved." He added that the uterus itself was very flaccid, very pale and bleeding very little. Apparently, circulation had stopped since no pulsations of the heart could be felt through the diaphragm although attempts were made to massage it.

These and other resuscitative efforts failed and the patient was pronounced dead.

Autopsy revealed marked bilateral pulmonary atelectasis, focal pulmonary emphysema and generalized vascular congestion. No other morphologic changes were found.

This was classified as a preventable anesthetic death. The amount of Pontocaine given is considerably more than is necessary for the satisfactory performance of a cesarean section, and in the absence of other information to explain the sudden death, it must be assumed that this overdose in hyperbaric solution rose to lethal levels when the patient's head was lowered. It is recognized that any form of anesthesia carries an inherent risk. This is increased when other agents (glucose) are added, for although the drug is *usually* fully fixed in twenty minutes, this is not necessarily always true. If the patient was already in slight Trendelenburg position, as seems likely, a heavy solution did not have far to go to kill her.

It is of further interest that this was the fourth cesarean section, thus adding further evidence to the already established fact that more than two or three sections vastly increase the risk of pregnancy. In 1954, 15 per cent of all maternal deaths in Massachusetts were associated with cesarean section, accounting for 25 per cent of the preventable deaths.

JOHN FIGGIS JEWETT, M.D.
Chairman

CORRESPONDENCE

PORTAL CIRCULATION

To the Editor: I have read with great interest Dr. Child's paper, "The Portal Circulation," which appeared in the May 19 issue of the *Journal*. I agree with most of his comments about the management of esophageal varices, and view portal decompression as the best available treatment for the patient with varices who has bled. Certainly, selection of patients with cirrhosis for such surgery on the basis of the criteria listed by the author as indicating a more favorable state of hepatic compensation is to be encouraged. In average hospital practice we unfortunately see patients whose evidence of hepatic decompensation, in addition to bleeding esophageal varices, makes them more serious risks as far as surgery is concerned.

Dr. Child disagrees with the contention of my colleagues and me, in our article, "Esophageal Varices without Hemorrhage in Cirrhosis: A proper indication for shunting procedures" (*New Eng. J. Med.* **250**:863-865, 1954), that portal decompression should sometimes be used in cirrhotic patients with varices who have not bled. We were led to our opinion by finding many cases of esophageal varices in esophagoscopic study of patients with biopsy-proved cirrhosis who had never had a hemorrhage. Some of these subsequently died in their first bout of hemorrhage. The question then arose concerning the frequency of death, with the measures for treatment available today, of the cirrhotic patient bleeding for the first time. In our own series, we found that close to 50 per cent of such patients died, directly or indirectly, in their first episode of bleeding, which often precipitated hepatic failure and coma in these fatal cases. From the very service that Dr. Child now heads at Boston City Hospital, Nachlas, O'Neil and Campbell, in a study entitled "The Life History of Patients with Cirrhosis of the Liver and Bleeding Esophageal Varices" (*Ann. Surg.* **141**:10-23, 1955), reported: "while it is frightening to realize that sixty percent of our bleeding cirrhotics will die of their first hemorrhage, it is also important to note that of the forty percent surviving the initial hemorrhage, only one-third will die during the subsequent year, and two-thirds will be alive longer than one year." A recent report by Atik and Simeone, from Cleveland City Hospital, on the subject "Massive Gastrointestinal Bleeding" (*Arch. Surg.* **69**:355-365, 1955), stated that 52 of 68 cirrhotic patients with bleeding varices died, a mortality of 77 per cent. The authors do not give the number of deaths from the first bleeding. What are we to do about the 50 or 60 per cent of patients who die of their first hemorrhage if the *sine qua non* for the indication of portal decompression is survival after a hemorrhage? The emergency portal decompression, which he presents as a suggestive approach, represents only a partial solution at best, but one that deserves more trial and one that we, too, have used in several cases. In our opinion, when esophagoscopy of a cirrhotic patient shows large varices involving at least two thirds of the esophagus, the chances for spontaneous disappearance seem to be somewhat remote. In an article, "On the Natural History of Esophageal Varices Secondary to Portal Cirrhosis. I. Observations on Spontaneous Changes in the Severity of Varices over Short Intervals (Less than a Year)" (*Gastroenterologia* **80**:257-262, 1953), Dr. Eddy D. Palmer and I reported on this aspect of esophageal varices; we believe that large varices probably do not undergo complete disappearance. Acknowledging the surgical mortality involved, we think that the patient with large varices will be a better risk before than after he bleeds. We also acknowledge the controversial nature of our opinion but point out that Dr. Blakemore has in his series a number of patients operated on before any bleeding. The high percentage of fatal cases in the first bleeding episode continues to concern us, and until we find out why varices bleed when they do, a basic unanswered question, we believe that selected prophylaxis may not be amiss. In our own series of patients with cirrhosis with varices who have not bled (to be reported in the *Southern Medical Journal*) we have performed portal decompression in only 18 of 87 patients. We are following all the available patients in this group by esophagoscopy and hope, in time, to have more definitive data on what happens to these patients with varices that have not bled. It has already been disconcerting to have lost some of this group in the first hemorrhage. The frank and basic questions that Dr. Child raises in his interesting article need to be answered. The use of varied approaches and diligent study of the natural course of the patient with varices who has not bled may supply some of the answers.

IRVING B. BRICK, M.D.
Associate Professor of Medicine
Georgetown University School of Medicine
Washington, D.C.

Dr. Brick's letter was submitted to Dr. Child, who made the following reply:

To the Editor: Needless to say, I have read Dr. Brick's letter with great interest. I was pleased indeed that he agreed with most of my comments on patients with esophagogastric hemorrhage from varices. Dr. Brick, of course, emphasizes with great clarity the controversial nature of one of the problems that currently confront those accepting the responsibility of caring for patients with cirrhosis and portal hypertension: what to advise for the patient who has varices but who has never bled. I must acknowledge, of course, that heretofore I have had no great enthusiasm for what might be called a prophylactic shunt. Nevertheless, I am quite willing to admit that as time goes on and more is learned, to use Dr. Brick's own words, of "the natural course of the patient with varices who has not bled," as well as "why varices bleed when they do," I may have to revise my present opinion. Because in Dr. Brick's own series only 18 of 87 patients with varices who have not bled have been operated on, I believe that there may be no very great disagreement between us.

After reflecting at length upon Dr. Brick's comments on mortality after first hemorrhage, I believe that I am again entitled to caution those interested in this subject against drawing inappropriate conclusions from published mortality figures after first hemorrhage without knowing in addition the degree of hepatic decompensation manifested by each patient concerned. In my opinion it is improper to consider

the degree of hepatic dysfunction equivalent in all patients who bleed from varices simply because cirrhosis happens to be the cause of their varices. Variations in hepatic reserve among patients with cirrhosis may be great indeed and obviously bear an important, but heretofore inadequately considered, relation to the rate of death after first and even subsequent hemorrhage. Certainly, mortality after portal decompression bears a direct relation to hepatic function.

Until we are in a position to correlate death from hemorrhage with hepatic function more accurately than is currently possible, a major part of our approach to variceal hemorrhage with cirrhosis will, I believe, continue to be imperfect. It is, of course, entirely possible that Dr. Brick and Dr. Palmer will answer some of these pressing questions in their forthcoming article in the *Southern Medical Journal.*

CHARLES G. CHILD, III, M.D.

Boston

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of the Boston City Hospital announces the schedule of the Tuesday evening lecture series to be held in the New Cheever Amphitheater, Dowling Building, Boston City Hospital, at 7 p.m. The program is as follows:

November 7. Melanotic Carcinoma. Sir Stanford Cade, K.B.E., C.B., F.R.C.S., senior surgeon, Westminster Hospitals, London, England.

November 15. Arterial Grafts in the Treatment of Diseases of the Major Arteries. Dr. Robert R. Linton, assistant professor of medicine, Harvard Medical School.

November 22. The Role of Surgery in the Treatment of Cancer. Dr. George Crile, Jr., surgeon, Cleveland Clinic.

November 29. Physiologic Changes during Infection. Dr. Edward Kass, assistant professor of medicine, Harvard Medical School.

December 6. Portal Systemic Encephalopathy in Liver Disease. Dr. Sheila Sherlock, London, England.

December 13. Heart Disease and Pregnancy. Dr. C. Sidney Burwell, professor of medicine, Harvard Medical School.

December 20. Current Concepts of the Sprue Syndrome. Dr. Chester M. Jones, professor of medicine, Harvard Medical School.

COURSE FOR LICENSED PRACTICAL NURSES

The only postgraduate course for licensed practical nurses offered in the eastern part of the country, which began on October 17 at the New England Hospital, will run for three months, offering experience in the operating room and recovery room and in the care of surgical and medical patients. The forty-hour week also includes four hours of instruction when the participants will attend grand rounds and weekly clinical conferences and will have special classroom work. A maximum of three weeks on evening duty and three weeks on night duty will be assigned for special experience and to give a total picture of the needs of patients. Additional experience may be provided, if desired, on an individual basis in the Out-Patient Department, central supply room and special diet kitchen.

Students will live in the Nurses' Home at the hospital and will receive a small stipend in addition to maintenance and tuition. Further information may be obtained from the New England Hospital Nursing Department, Dimock Street, Roxbury.

SOUTH END MEDICAL CLUB

The monthly meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 15, at 12 noon.

Dr. Herbert D. Adams will talk on "The Management of Carcinoma of the Lung." All physicians are invited to attend.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Massachusetts General Hospital and the Peter Bent Brigham Hospital in the Morse Auditorium, Museum of Science, Science Park, Boston, on Monday, November 14, 1955, at 8 p. m.

PROGRAM

Massachusetts General Hospital, Edward F. Bland, M.D., presiding:

Cardiorespiratory Problems in Severe Poliomyelitis Observed during the Recent Epidemic. Frank K. Austen, M.D., Jan Koch-Weser, M.D., and Richard A. Field, M.D.

Usefulness of Serum Transaminase Determinations in the Diagnosis of Myocardial Infarction. Charles H. DuToit, M.D.

Myxoma of the Left Atrium Successfully Removed. Gordon G. Scannell, M.D.

Peter Bent Brigham Hospital, Samuel A. Levine, M.D., presiding:

Hepatomegaly — A Sign of Left Ventricular Failure in Atrial Septal Defect. Hiroshi Kuida, M.D., Paul Novack, M.D., Florence W. Haynes, M.D., Ph.D., Leonard A. Cobb, M.D., and Lewis Dexter, M.D.

Mechanism of Paroxysmal Auricular Tachycardia with Block. Bernard Lown, M.D.

A Pickwickian Syndrome. C. Sidney Burwell, M.D., Eugene D. Robin, M.D., Albert G. Bickelman, M.D., and Robert Whaley, M.D.

At 7:30 p. m., for the benefit of those who wish to attend, the Museum of Science will arrange a special showing of the "transparent woman" in the second-floor exhibit hall.

Free parking privileges are available on the premises at Science Park (emergency telephone number, RIchmond 2-1410).

Interested physicians and medical students are cordially invited to attend.

MASSACHUSETTS PHYSICIANS CLUB

There will be a meeting of the Massachusetts Physicians Club at the Hotel Kenmore, Boston, Tuesday, November 8, at 8:30 p.m.

Dr. Dwight E. Harken will give a talk entitled "Progress Report on Heart Surgery."

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 4–30. Consultation Clinics for Crippled Children in Massachusetts. Page 744, issue of October 27.

NOVEMBER 4 and 5. American Society of Tropical Medicine and Hygiene. Page 624, issue of October 6.

NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

NOVEMBER 7. Massachusetts Heart Association. Page 745, issue of October 27.

NOVEMBER 7, 15, 22 and 29 and DECEMBER 6, 13 and 20. Boston City Hospital House Officers' Association. Notice above.

NOVEMBER 7 and DECEMBER 5, 1955, and JANUARY 16, FEBRUARY 6, MARCH 5 and APRIL 2, 1956. Fried Lecture Series. Page 535, issue of September 22.

NOVEMBER 7–9. Association of Military Surgeons of the United States. Page 118, issue of July 21.

NOVEMBER 7, 21 and DECEMBER 5, 1955, and JANUARY 16, 1956. Hartford Medical Society. Page 708, issue of October 20.

NOVEMBER 8. Harvard Medical Society. Page 708, issue of October 20.

NOVEMBER 9, 1955–MAY 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.

NOVEMBER 10–12. American College of Cardiology. Page 394, issue of September 1.

NOVEMBER 11 and 12. Inter-Society Cytology Council. Page 745, issue of October 27.

NOVEMBER 14. New England Cardiovascular Society. Notice above.

NOVEMBER 14 and 18. American Public Health Association. Page 578, issue of September 29.

NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

NOVEMBER 15. South End Medical Club. Notice above.

NOVEMBER 17 and DECEMBER 15. Arthritis Study Unit. Page 668, issue of October 13.

NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

NOVEMBER 27 and 28. American College of Chest Physicians. Page 578, issue of September 29.

NOVEMBER 28–DECEMBER 2. Interim Session of the American Medical Association, Boston.

NOVEMBER 30, 1955, and JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

DECEMBER 5–14, 1955, and JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

DECEMBER 7, 1955, and JANUARY 25, FEBRUARY 29, MARCH 21 and APRIL 25, 1956. Massachusetts Heart Association. Page 623, issue of October 16.

DECEMBER 9 and 10. Association for Research in Nervous and Mental Disease. Page 745, issue of October 27.

DECEMBER 14, 1955, and FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 203, issue of August 4.

JANUARY 20–27, 1956. Fifth Panamerican Congress of Gastroenterology. Page 746, issue of October 27.

MARCH 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.

MAY 3–5, 1956. American Goiter Association. Page 348, issue of August 25.

MAY 28–JUNE 1, 1956. European Symposium on Vitamin B. Page 578, issue of September 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 10

THURSDAY, NOVEMBER 10

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:15 a.m.–12:00 m. Thoracic Conference. Case Presentations of Medical and Surgical Interest. Drs. Harken and Black. Amphitheater, Peter Bent Brigham Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.
*8:30 p.m. Fried Lecture Series. Surgical and Medical Management of Advanced Malignant Disease. Dr. J. Englebert Dunphy. Usen Auditorium, Newton-Wellesley Hospital, Wellesley.

FRIDAY, NOVEMBER 11

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, NOVEMBER 12

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten and staff. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Thibodeau and staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, NOVEMBER 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Therapeutic Conference. Dr. McCombs, moderator. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference, Mortality and Morbidity. Dr. Orr. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.
*8:00 p.m. New England Cardiovascular Society. Morse Auditorium, Museum of Science, Science Park, Boston.

TUESDAY, NOVEMBER 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic, Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
12:00 m. South End Medical Club. Boston Tuberculosis Association, 554 Columbus Avenue, Boston.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*4:00–5:00 p.m. Surgical Pathological Conference. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten and staff. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, NOVEMBER 16

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–1:00 p.m. Postgraduate Medical Institute. Bleeding in the Last Trimester of Pregnancy and its Complications. Drs. Hindman and Stone. St. John's Hospital, Lowell.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery, and Psychiatry Conference. Drs. Sullivan, B. Selverstone and Hope. Stearns Auditorium, New England Center Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*2:00–4:00 p.m. Postgraduate Medical Institute. The Use and Abuse of the Electrocardiogram in the Diagnosis of Cardiac Disease. Drs. Littmann, Williams and Wolff. Lemuel Shattuck Hospital, Jamaica Plain.
*2:00–4:00 p.m. Postgraduate Medical Institute. Pneumonia or Pneumonitis. Drs. Pittman and Scannell. Norfolk County Hospital, Braintree.
*2:00–4:00 p.m. Postgraduate Medical Institute. Personality Changes in Middle Life. Drs. Gair and Kozol. St. Luke's Hospital, New Bedford.
*2:00–5:00 p.m. Postgraduate Medical Institute. Adrenal Diseases. Drs. Desautels, Goldfien and Hamolsky. Burbank Hospital, Fitchburg.
*3:00–5:00 p.m. New England Conference on Allergy and Related Subjects. New England Medical Center, 37 Bennet Street, Boston.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*4:00–6:00 p.m. Postgraduate Medical Institute. Gynecologic Problems in Adolescence. Drs. Brown and Duncan. St. Luke's Hospital, Pittsfield.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.

NOW...
Federal law permits oral prescription

your best bet!

Syrup and oral tablets. Each teaspoonful or tablet of HYCODAN contains 5 mg. dihydrocodeinone bitartrate and 1.5 mg. Mesopin.** May be habit-forming. Average adult dose, 1 teaspoonful or 1 tablet after meals and at bedtime.

**Homatropine Methylbromide

Hycodan®*

(Dihydrocodeinone with Homatropine Methylbromide)

BETTER THAN CODEINE **FOR COUGH**[1]

FASTER
LONGER-LASTING
MORE THOROUGH

BETTER THAN CODEINE *PLUS* APC **FOR PAIN**[2]

Percodan®†

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC)

Scored, yellow oral tablets. May be habit-forming. Average adult dose, 1 tablet q. 6 h.

1. Hyman, S., and Rosenblum, S. H.: Illinois M. J. 104:257, 1953.
2. Piper, C. E., and Nicklas, F. W.: Indust. Med. 23:510, 1954.

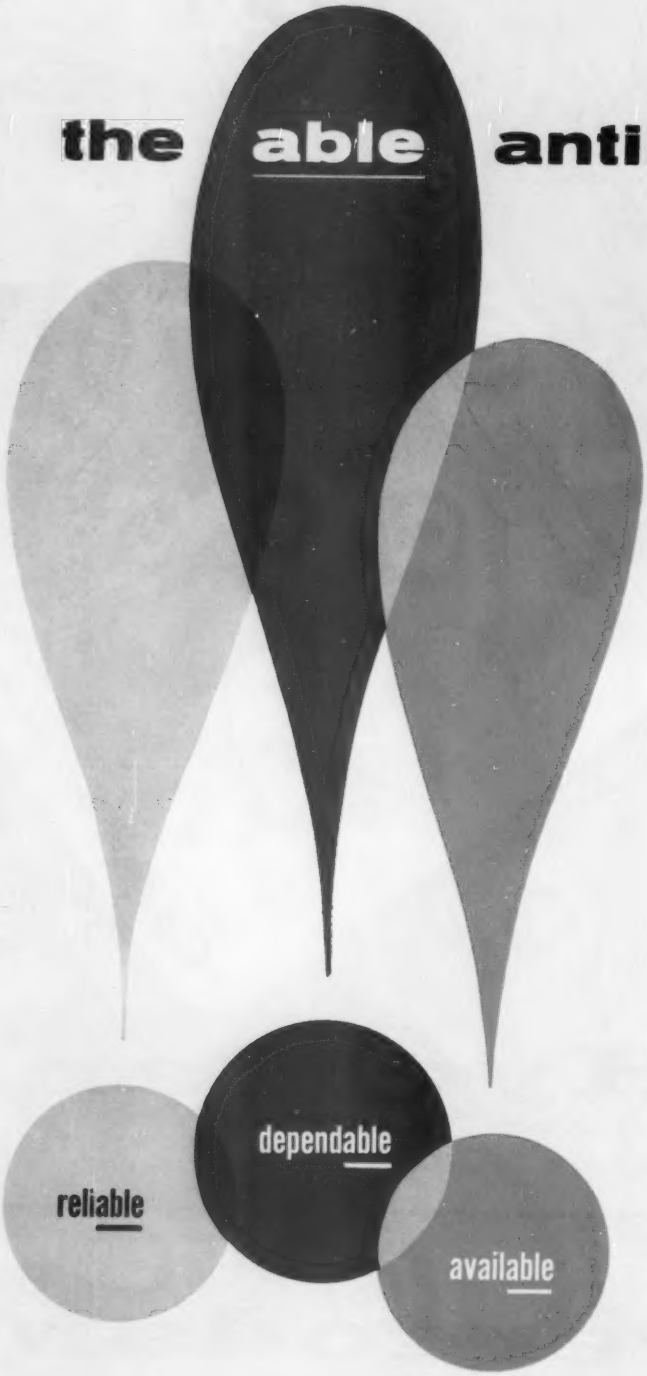
*U.S. Pat. 2,630,400
†U.S. Pat. 2,628,185

Endo®

Literature? write
ENDO PRODUCTS INC.
RICHMOND HILL 18, NEW YORK

the able antibiotic

AC



CHROMYCIN*

Tetracycline LEDERLE

dependable action
Rapid diffusion and penetration, prompt control of infection, negligible side effects. Proved against Gram-positive and Gram-negative bacteria, rickettsia, and certain viruses and protozoa.

reliable quality
Made in Lederle's *own* laboratories under exacting quality controls, and distributed only under the Lederle label.

available in "most-used" forms
You can choose the *right* dosage form to suit the patient's needs and comfort, and your convenience.

SF

ACHROMYCIN with STRESS FORMULA VITAMINS

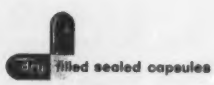
SF

Newest ACHROMYCIN dosage form!
Exclusive dry-filled, sealed capsules!

Stress formula suggested by the National Research Council. ACHROMYCIN SF provides potent anti-infective action, plus nutritional supplementation to hasten recovery. Particularly useful in prolonged illness. More effective because powder-filled, soft gelatin capsules are rapidly and completely absorbed. No oils, no paste . . . tamperproof!

Capsules of 250 mg.

Also available: ACHROMYCIN SF Oral Suspension, 125 mg. per teaspoonful (5 cc.)



LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

Lederle

An effective and agreeable way to give penicillin...

Penalev®

SOLUBLE TABLETS CRYSTALLINE POTASSIUM PENICILLIN G

MAJOR ADVANTAGES: Six dosage strengths for maximum flexibility of dosage. Ideally suited to pediatrics—in rheumatic fever prophylaxis, and wherever oral penicillin is indicated. Tablets dissolve readily in water, milk, juices, infant formulas.

Supplied. Soluble Tablets of 50,000, 100,000, 200,000, 250,000, 500,000 and 1,000,000 units of potassium penicillin G.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF
MERCK & CO., INC.

Serpasil®
(reserpine CIBA)

Elixir

Sedation without hypnosis

MEDICAL HORIZONS TV Monday P.M.

Index to Advertisers

	PAGE
Abbott Laboratories	xviii, xix, xxxiv, xxxv
American Meat Institute	viii
American Hospital Supply Corp.	iii
Ames Company, Inc.	xii
The Armour Laboratories	xxxvi
Baldpate, Inc.	xl
Baxter Laboratories, Inc.	iii
Boston Medical Laboratory	xxxviii
Brewer & Company, Inc.	xi
The Channing Home	xxxiv
Ciba Pharmaceutical Products, Inc.	ii, xxvi, xxvii
Crosbie-Macdonald	xxx
David Memorial Nursing Home	xl
Davies, Rose & Company, Limited	xxxi
Eaton Laboratories	x
Electroencephalographic Laboratory, Inc.	xxxviii
Endo Products, Inc.	xxiii
Ethicon, Inc.	After xxxviii
Fine Chemicals	xlii, xliii
Glenside, Inc.	xl
Gray Pharmaceutical Co., Inc.	xxix
Hoffmann-La Roche, Inc.	After xxx
Chas. B. Knox Gelatine Company, Inc.	xxi
Lakeside Laboratories, Inc.	xiv
Leary Laboratory	xxxviii
Lederle Laboratories	xxiv, xxv, xli
Eli Lilly and Company	Front Cover
The S. E. Massengill Company	xxxix

	PAGE
Mead Johnson & Company	Back Cover
The Medical Protective Company	xxxvi
The Wm. S. Merrell Company	xxxiii
Mount Auburn Hospital	xxxiv
The New Orleans Graduate Medical Assembly	xxxv
T. J. Noonan Co.	xxxv
Perkins School	xl
Pfizer Laboratories (Div. of Chas. Pfizer & Co., Inc.)	iv, v, xl, xli
Ring Sanatorium	xl
A. H. Robins Co., Inc.	After vi
J. B. Roerig Co.	vii
Schering Corporation	xv
Sharp & Dohme (Div. of Merck & Co., Inc.)	vi, xxvi, xxx
Smith, Kline & French Laboratories	xvi
E. R. Squibb & Sons (Division of Mathieson Chemical Corp.)	xxxii
Storrow House (Massachusetts General Hospital)	xl
U. S. Vitamin Corporation	xx
The Upjohn Company	ix, xiii, xxxvii
Washingtonian Hospital	xxxiv
Westwood Lodge, Inc.	xl
White Laboratories, Inc.	xxviii
Winthrop-Stearns, Inc.	xxii
Wiswall Sanatorium	xl
Woodside Cottages, Inc.	xl
Wyeth Laboratories	xvii

CIBA

SUMMIT, NEW JERSEY

Nonsoporific tranquilizer

Especially indicated for Old People and Children

Highly compatible vehicle

New SERPASIL ELIXIR is compatible with Pyribenzamine® Elixir, dextro-amphetamine sulfate elixir, Antrenyl® Syrup, codeine phosphate, ephedrine sulfate, sodium salicylate and many other medications. Serpasil Elixir has a clear light-green color and a pleasant lemon-like flavor. Each 4-ml. teaspoonful contains 0.2 mg. of Serpasil.

in gestation

. . . nowhere will you find so much protection by such small guardians

two-a-day

GESTATABS

. . . the Mol-Iron® prenatal supplement . . . provide

✻ **Protection** from iron deficiency anemia with prophylactic Mol-Iron

✻ **Protection** from leg cramps during pregnancy with phosphorus-free calcium

✻ **Protection** from neonatal prothrombin deficiency with vitamin K.

The comprehensive formula of Gestatabs satisfies the nutritional demands of pregnancy—thus reducing complications, aiding delivery and improving lactation.

Vitamin A	6,000 U.S.P. Units
Vitamin D	600 U.S.P. Units
Vitamin K (Menadione)	2 mg.
Vitamin B_{12} Activity Equivalent*	2 mcg.
Folic Acid	1 mg.
Ascorbic Acid	100 mg.
Thiamine Mononitrate	3 mg.
Riboflavin	5 mg.
Pyridoxine Hydrochloride	1.5 mg.
Calcium Pantothenate	10 mg.
Nicotinamide	30 mg.
Mol-Iron	
Ferrous Sulfate	120 mg.
Molybdenum Oxide	1.8 mg.
Calcium (Elemental)**	380 mg.

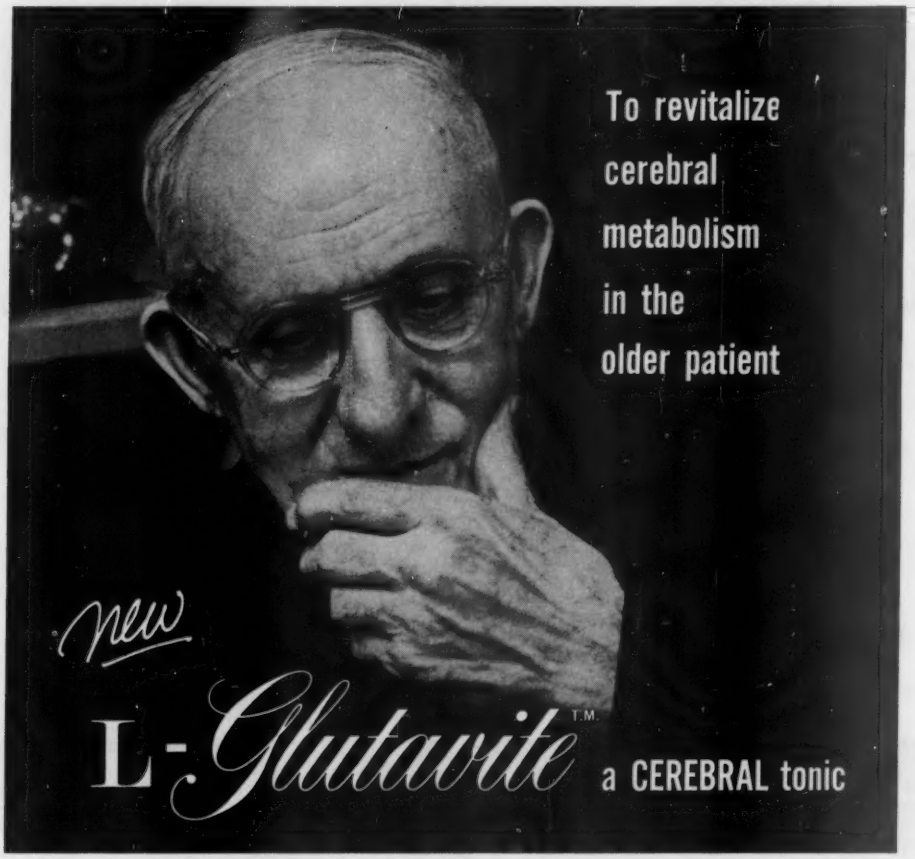
*As in Streptomyces fermentation extractives.

**Phosphorus-free from calcium gluconate and calcium carbonate.

—supplied in bottles of 60 (one month's supply) and 1000 tablets.

Also, Mol-Iron with Calcium and Vitamin D, capoule-shaped tablets—for treatment of anemia of pregnancy.

WHITE LABORATORIES, INC.
Kenilworth, N. J.



L-Glutavite is specifically formulated to assist in the treatment of geriatric patients whose symptoms of weakness, apathy and fatigue are characteristic of waning cerebral metabolism. Himwich[1] reports excellent results with sodium glutamate in such cases, while Lehmann states that "a trial with nicotinic acid is always indicated . . ."[2] By combining these key factors with other vital nutritional elements, L-Glutavite effectively increases cerebral blood flow while it enhances the ability of cerebral tissue to utilize the increased nutrients provided. This unique therapeutic formula helps the tired, the apathetic, the depressed individual to face life more actively, and with greater interest.

Supplied in cartons of 30 individual dosage packets; initial dose, 3-5 packets per day for 5 to 6 weeks. Pleasant-tasting appetite-stimulating powder, to be mixed in fruit juices or sprinkled on food. Contains monosodium L-glutamate, niacin, thiamine, riboflavin, ascorbic acid, ferrous sulfate and dicalcium phosphate, in high potencies.

1. Himwich H.E.: Paper presented at American Psychiatric Association meeting, St. Louis, May, 1954.
2. Lehmann, H.: 27th Annual Conference, Milbank Memorial Fund, New York, Paul B. Hoeber, Inc., 1952, p. 587.

GRAY PHARMACEUTICAL CO., INC., Newton 58, Massachusetts

1950 Cortone® | 1952 Hydrocortone®
1954 'Alflorone' | 1955 'Hydeltra'

DELTRA® tablets

(Prednisone, Merck) 5 mg. - 2.5 mg. - 1 mg. (scored)

the delta-1 analogue of cortisone

SHARP & DOHME
Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

Indications:
Rheumatoid arthritis
Bronchial asthma
Inflammatory skin conditions

PHYSICIANS' LIABILITY INSURANCE

Are Your Limits Adequate?

Quality and Service Purchased Through a Well Established Agency

Write to us for Rates

CROSBIE-MACDONALD

GEORGE H. CROSBIE · EDWARD J. O'NEIL, JR. · ARTHUR H. CROSBIE

79 Milk St.
BOSTON 9

Telephone
LI 2-9538

shot at sunrise —

The most annoying of calls to administer a narcotic is the call that comes in the early morning hours. Levo-Dromoran can be given orally to obtain longer and more complete pain relief than morphine by injection.

Levo-Dromoran® Tartrate 'Roche' - brand of levorphan tartrate

Hoffmann - La Roche Inc · Nutley · N.J.

To relieve/prevent

postoperative cough—

ROMILAR 'Roche' is a new, non-narcotic cough specific, especially useful following inhalation anesthesia. Ten mg equals 15 mg of codeine in cough-suppressant effect - yet Romilar avoids central depression, nausea, anorexia and constipation.

Romilar® Hydrobromide - brand of dextromethorphan hydrobromide - tablets, 10 mg; syrup, 10 mg/4 cc

Hoffmann - La Roche Inc • Nutley • N.J.

THIS DR

is the **symbol**

of the

STANDARDIZED

Tablets

QUINIDINE SULFATE

NATURAL

0.2 Gram

(approx. 3 grains)

produced by

Davies, Rose & Co., Ltd.

By specifying the name the physician will be assured that this standardized form of Quinidine Sulfate Natural will be dispensed to his patient.

Clinical samples sent to physicians on their request

Davies, Rose & Company, Limited
Boston 18, Massachusetts

Q4

Alkaloidally assayed and standardized, insuring uniformity and therapeutic dependability

Each tablet contains 0.2 Gram (approx. 3 grains) and is scored for the convenient administration of half dosages.

Supplied also in strengths of 0.12 Gram (approx. 2 gr.) and 0.3 Gram (approx. 5 gr.)

Mysteclin

STECLIN-MYCOSTATIN
SQUIBB TETRACYCLINE-NYSTATIN

WELL TOLERATED BROAD SPECTRUM ANTIBACTERIAL THERAPY PLUS ANTIFUNGAL PROPHYLAXIS

BROAD SPECTRUM ANTIBIOTIC THERAPY, EFFECTIVE IN MANY COMMON INFECTIONS

Because it contains Steclin (Squibb Tetracycline), MYSTECLIN is an effective therapeutic agent for most bacterial infections. When caused by tetracycline-susceptible organisms, the following infections are a few of those which can be expected to respond to MYSTECLIN therapy:

bronchitis	gonorrhea	osteomyelitis	pyelonephritis
colitis	lymphadenitis	otitis media	sinusitis
furunculosis	meningitis	pneumonia	tonsillitis

MYSTECLIN is also indicated in certain viral infections and in amebic dysentery.

BROAD SPECTRUM ANTIBIOTIC THERAPY, WITH A MINIMUM OF SIDE EFFECTS

In clinical use, Steclin has produced an extremely low incidence of the gastrointestinal distress sometimes observed with other broad spectrum antibiotics. Mycostatin (Squibb Nystatin), as contained in MYSTECLIN, is also a particularly well tolerated antibiotic and has produced no allergic reactions, even after prolonged administration.

BROAD SPECTRUM ANTIBIOTIC THERAPY, WITHOUT THE DANGER OF MONILIAL OVERGROWTH

Because it contains Mycostatin, the first safe antifungal antibiotic, MYSTECLIN effectively prevents the overgrowth of Candida albicans (monilia) frequently associated with the administration of ordinary broad spectrum antibiotics. This overgrowth may sometimes cause gastrointestinal distress, anal pruritus, vaginitis, and thrush; on occasion, it may have serious and even fatal consequences.

SQUIBB

Each MYSTECLIN capsule contains 250 mg. Steclin Hydrochloride and 250,000 units Mycostatin.

Minimum adult dose: 1 capsule q.i.d.

Supply: Bottles of 12 and 100.

"MYSTECLIN", "STECLIN" AND "MYCOSTATIN"® ARE SQUIBB TRADEMARKS

Kolantyl
+ diet

= complete ulcer therapy

provides prolonged relief of ulcer pain.[1]

Kolantyl: 1. Neutralizes acid, 2. Inhibits pepsin, 3. Relieves hypermotility and spasm through musculotropic action, 4. Relieves spasm through neurotropic action, 5. Forms protecting demulcent, 6. Inhibits lysozyme.

This combination of ulcer-combating ingredients in pleasant-tasting KOLANTYL Gel, or convenient tablets, makes rational its use as the medication of choice in peptic ulcer therapy.

Rx Information

Kolantyl

Gel and Tablets

Action:

*Bentyl** content affords spasmolysis and parasympathetic-depressant actions without the side effects of atropine.

Rapid, Prolonged Antacid Relief ... Balanced antacids — no laxation — no constipation

Proven Demulcent Action ... Helps protect normal cells, encourages cellular repair

Anti-enzyme Action ... Necrotic pepsin and lysozyme action checked

Composition:

Each 10 cc. of KOLANTYL Gel or each KOLANTYL tablet contains:

Bentyl Hydrochloride	5 mg.
Aluminum Hydroxide Gel	400 mg.
Magnesium Oxide	200 mg.
Sodium Lauryl Sulfate	25 mg.
Methylcellulose	100 mg.

Dosage:

Gel — 2 to 4 teaspoonfuls every three hours, or as needed. Tablets — 2 tablets (chewed for more rapid action) every three hours, or as needed.

Supplied:

Gel — 12 oz. bottles. Tablets — bottles of 100 and 1,000.

1. Johnston, R.L.: J. Indiana St. M.A. 46:869, 1953. 2. McHardy, G., and Browne, D.: Southern M. J. 45:1139, 1952.

*Merrell's distinctive antispasmodic that is more effective than atropine—free from side effects of atropine.[2]

THE WM. S. MERRELL COMPANY
New York • CINCINNATI • St. Thomas, Ontario

Merrell Since 1828

Pioneer in Medicine for Over 125 Years

T.M. 'BENTYL', KOLANTYL®

MOUNT AUBURN HOSPITAL

announces a course in

ELECTROCARDIOGRAPHY

by

Richard A. Bloomfield, M.D.

starting January 11, 1956
for sixteen sessions
on Wednesdays

ADVANCED COURSE - 2-3 P.M.

Margaret Jewett Hall

Enrollment Limited

Tuition — $50.00

Mail checks to

Director's Office
Mount Auburn Hospital

THE CHANNING HOME

For the MEDICAL and SURGICAL treatment of Pulmonary Tuberculosis in Women

Established 1857

198 Pilgrim Road, Boston 15, Mass.

Our endowment permits variations in charges for patients' board. There are no physicians' fees.

Good nursing care and food are emphasized.

Address all applications to:
ELIZABETH H. PELTON, Superintendent

Washingtonian Hospital

41 Morton Street, Boston 30, (Jamaica Plain) Mass.
Incorporated 1859

Conditioned Response, Psychotherapy, Antabuse, Adrenal Cortex and other drug therapies, Semi-Hospitalization for Rehabilitation of Male and Female Alcoholics.

Treatment of Acute Intoxication and Alcoholic Psychoses Included

State Outpatient Clinic and Social Service Department for Male and Female Patients

Joseph Thimann, M.D., *Medical Director*
Consultants in Medicine, Surgery and the other Specialties
Telephone JA 4-1540

PLAN NOW TO ATTEND

The Nineteenth Annual Meeting of
The New Orleans Graduate Medical Assembly

FEBRUARY 27, 28, 29 and MARCH 1, 1956

* * *

EIGHTEEN OUTSTANDING GUEST SPEAKERS
CLINICOPATHOLOGIC CONFERENCES
OVER 100 TECHNICAL EXHIBITS
THREE ROUND-TABLE LUNCHEONS
MEDICAL MOTION PICTURES
COLOR TELEVISION
SYMPOSIA

ALL-INCLUSIVE REGISTRATION FEE, $20.00

* * *

THE POSTCLINICAL TOUR TO THE WEST INDIES AND CENTRAL AMERICA BY PLANE
visiting
PUERTO RICO — VIRGIN ISLANDS — HAITI — JAMAICA — PANAMA — GUATEMALA
leaving from New Orleans on March 2

For information concerning the Assembly meeting and tour, write
SECRETARY, ROOM 103, 1430 TULANE AVENUE
NEW ORLEANS 12, LOUISIANA

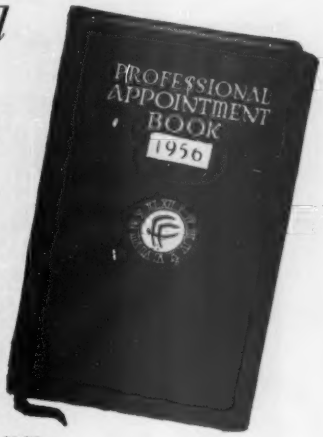
Keep Ahead

ORDER YOUR
FAWCETT'S
Now!

Contains **Daily Pages** with ½ hr. appointment spaces, columns for credits and debits, and monthly calendars;

Monthly Summary pages to record income, expense and net income computations;

Yearly Summary page showing your financial status at a glance. A simple method of recording data for income tax purposes. Handsomely bound. **$2.25**



Phone for quick delivery

T. J. Noonan Co.

HOSPITAL · LABORATORY · MEDICAL · SURGICAL · SUPPLIES · T. J. NOONAN CO.

Phone, JAmaica 2-8700 • Ample Parking

408 South Huntington Avenue
Jamaica Plain (Boston 30), **Mass.**

Albany, New York, Branch
579 New Scotland Ave. Phone, Albany 89-2508

new nonbarbiturate

Placidyl

Trademark

nudges your patient to sleep

patients with nervous insomnia
sleep naturally within 15 to 30
over. Not contraindicated in
of liver or kidney disease.
bottles of 100.

Abbott

IN CORTICOID-TREATED PATIENTS

minimize adrenal suppression and atrophy

BY THE REGULAR PERIODIC USE OF

HP*ACTHAR® *Gel*

Stress of surgery, accidents or infections is magnified in patients treated with cortisone, hydrocortisone, prednisone or prednisolone. Adrenal steroids, even in small doses, jeopardize the defense mechanism against stress by causing adrenal cortical atrophy. Concomitant use of HP*ACTHAR *Gel* counteracts adrenal atrophy by its stimulant action on the adrenal cortex.

Dosage recommendations for supportive HP*ACTHAR *Gel* are, inject:

1 a. 100 to 120 U. of HP*ACTHAR *Gel* for every 100 mg. of prednisone or prednisolone.

b. 100 U. of HP*ACTHAR *Gel* for every 200 to 300 mg. of hydrocortisone.

c. 100 U. of HP*ACTHAR *Gel* for every 400 mg. of cortisone.

2 Discontinue use of steroid on the day of injection.

*Highly Purified. HP*ACTHAR *Gel* is The Armour Laboratories brand of purified corticotropin.

THE ARMOUR LABORATORIES

A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

THE MEDICAL PROTECTIVE COMPANY

FORT WAYNE, INDIANA

the doctor's most secure source of security

PROFESSIONAL PROTECTION EXCLUSIVELY SINCE 1899

BOSTON Office:
Augustus F. Fox,
Representative,
11 Pemberton Square,
Tel. CApitol 7-0119

OPENING IN NEW MEDICAL BUILDING now under construction in Boston suburb. Dermatologist preferred, but will consider others. Owned by medical group, opportunity to become part-owner. Address A51, *New Eng. J. Med.* 18-3t

SANBORN Plastic Case Model Cardiette, excellent condition. $100.00. Call Brockton, Mass. 9410. B69-18-2t

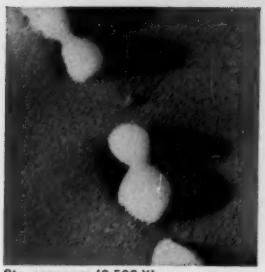
FOR SALE OR RENT — Ten-room house at Doctor's Row, 167 Maple Street. Occupied now as home and office. Moving to Florida. Will turn over well-established practice to suitable physician. Property can accommodate four doctors. Parking facilities good. This is a sound investment. Write or call James G. Makol, M.D., 167 Maple Street, Springfield 5, Massachusetts. Telephone RE 6-5175 or 6-0408. B70-18-4t

FOR SALE — X-ray. 100 MA combination fluoroscopic and radiographic tilt table with Bucky diaphragm. Complete darkroom accessories. Price reasonable. Call ALgonquin 4-5611. B71-18-3t

(Additional advertisements on page xxxviii)

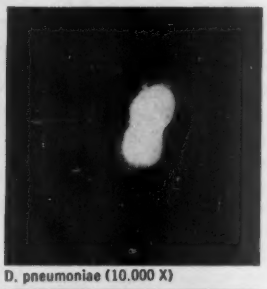
The organisms commonly involved in

Tracheobronchitis

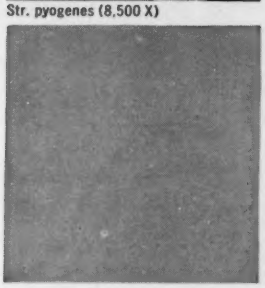


Str. pyogenes (8,500 X)

Staph. aureus (9,000 X)

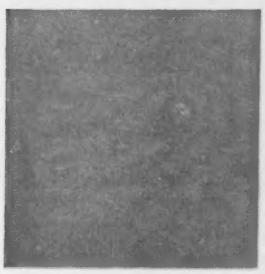


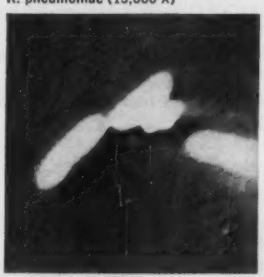
D. pneumoniae (10,000 X)



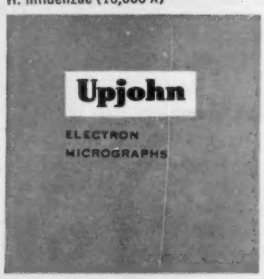
K. pneumoniae (13,000 X)

H. influenzae (16,000 X)





H. pertussis (7,500 X)



***All* of them are included in the more than 30 organisms susceptible to broad-spectrum**

PANMYCIN®

HYDROCHLORIDE

100 mg. and 250 mg. capsules • 125 mg. and 250 mg./tsp. oral suspension (PANMYCIN Readimixed)
100 mg./cc. drops • 100 mg./2 cc. injection, intramuscular
100 mg., 250 mg., and 500 mg. vials, intravenous

®TRADEMARK, REG. U.S. PAT. OFF.—THE UPJOHN BRAND OF TETRACYCLINE

PROTEIN BOUND AND TOTAL IODINE
PAPER ELECTROPHORESIS
CATECHOL-AMINES
STEROID & CLINICAL CHEMISTRY

BOSTON MEDICAL LABORATORY

NORBERT BENOTTI — JOSEPH BENOTTI
DIRECTORS

19 BAY STATE ROAD, BOSTON 15, MASS.

KEnmore 6-0348 — 0533

PHYSICIANS' Office FURNITURE. All standard lines, new. Used equipment from time to time. Convenient terms. Visit our showroom close by Veterans Hospital. Ample parking. T. J. NOONAN Co., 408 South Huntington Avenue, Jamaica Plain (Boston 30), Mass. Phone JAmaica 2-8700 for literature. Medical, hospital, laboratory, sickroom supplies. B260-20-tf

AVAILABLE IMMEDIATELY — 1180 Beacon Street, Brookline, Mass. 3 rooms. Waiting room shared with one physician. 24-hour switchboard available. Suitable for internist, surgeon or dentist. Please call, ASpinwall 7-8332. B57-12-tf

OFFICE FOR RENT in professional building on Marlborough Street. 3 and 5 rooms. Elevator and janitor service. Reasonable rent. Further information, FAirview 3-3480. B33-7-tf

BIND your *New England Journal of Medicine*. Make it a permanent part of your library—for easy reference and lasting wear. In full black library buckram, only $3.30 per volume, plus shipping charges. All other journals and periodicals bound also. Inquiries invited. Norden Bindery, 2100 West Grand Avenue, Chicago 12, Ill. B300-14-tf

UNITED LIMB & BRACE CO., Inc., manufacturers of artificial limbs. 61 Hanover Street, Boston, CA 7-2183. B517-6-tf

MEDICAL DIRECTOR — Experienced in geriatrics rehabilitation, medical administration. 600-bed chronic disease hospital in New England. Apply by letter stating qualifications. Address A18, *New Eng. J. Med.* 18-tf

MEDICAL SECRETARY desires position in Brookline - Boston area. Available immediately. 15 years' experience. Address A47, *New Eng. J. Med.* 18-2t

LEARY LABORATORY
43 BAY STATE ROAD
BOSTON, MASSACHUSETTS
OLGA C. LEARY, M.D.
OLGA LEARY, JR., M.D.
Dependable and Rapid Laboratory Service. All Branches
Containers furnished
Tel. KE 6-2121

FINEST BEACON STREET, BROOKLINE LOCATION — Three-room suite. Call AS 7-2944. B30-6-tf

NISSEN'S INSTITUTE OF PHYSICAL THERAPY, 1126 Boylston Street, Boston, KE 6-1030. Cape Cod office, Route 28, West Harwich. Telephone Harwich 984. B290-3-tf

FOR SALE — Large general practice, home, complete equipment and offices. Over $100 derived monthly from property. No charge for practice itself. New Hampshire town. Leaving to specialize. Address A246, *New Eng. J. Med.* 22-tf

BAR HARBOR, MAINE — For sale — Doctor's home and connecting offices consisting of waiting room, examining room, treatment room, large laboratory and storage room. Used as home for 35 years. Making this unusual opportunity to continue an established location. Address A21, *New Eng. J. Med.* 6-tf

ELECTROENCEPHALOGRAPHIC LABORATORY, INC.
270 COMMONWEALTH AVE., BOSTON KE 6-8100
Electroencephalograms
Electromyograms

POSITION OPEN at Boston Long Island Hospital. Assistant resident physician, $94 per week plus maintenance. Vacation and sick-leave benefits. Write Superintendent, Long Island Hospital, Boston 69, Mass. B68-17-4t

MEDICAL SECRETARY, experienced, would like a position in psychiatrist's office in Boston, Massachusetts. Address A48, *New Eng. J. Med.* 18-1t

WELL-TRAINED CLASS A GRADUATE desires part-time clinic or other work. Experienced in industrial medicine. Program flexible. Address A49, *New Eng. J. Med.* 18-2t

PEDIATRICIAN, certified, married, age 33, desires location or association, available Spring, 1956. Address A50, *New Eng. J. Med.* 18-4t

RESIDENT PHYSICIAN
Position available shortly after the first of next year for psychiatrist in small but active private mental hospital 15 miles from Boston. Secluded private residence available. Position offers good future possibilities. All replies strictly confidential. Write giving full information to:

Box A 52
N. E. Journal of Medicine
8 Fenway, Boston 15, Massachusetts

OFFICE AND EXAMINING ROOM available for M.D. Bay State Road. Share laboratory, secretary, waiting room. COmmonwealth 6-0157. B43-17-2t

LABORATORY TECHNICIANS, registered M.T. (ASCP) preferred, male or female, for growing laboratory service in a 200-bed New England hospital. New, completely equipped laboratory. Salary open according to ability and experience. Address A28, *New Eng. J. Med.* 9-tf

GENERAL PRACTITIONERS AND INTERNISTS to associate with medical group; modern well-equipped facilities; excellent educational opportunities; paid annual vacation and study period. Net income $12,000 to $25,000 depending upon training and experience. Reply Box 406, California, Pennsylvania. B38-8-tf

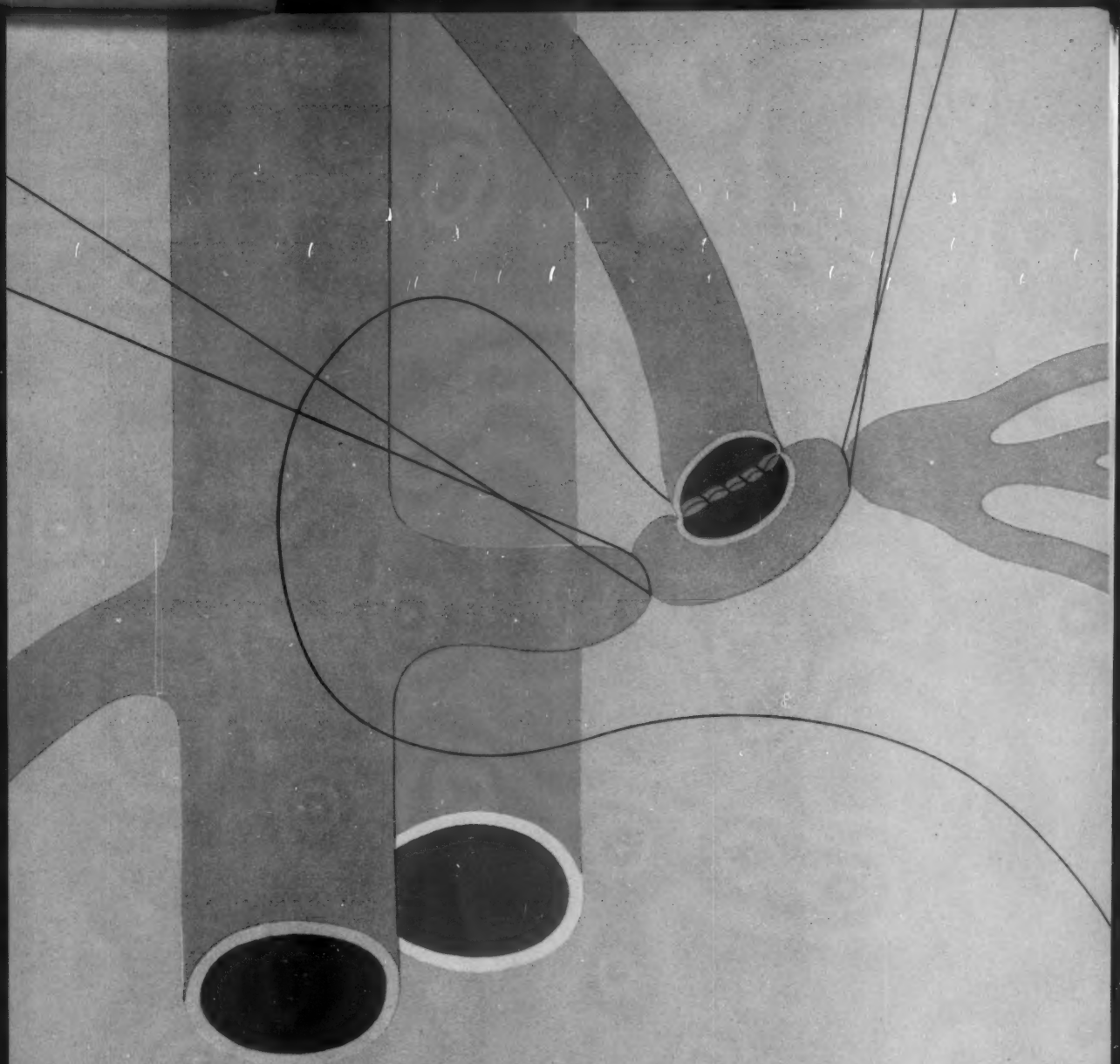
NEW MEDICAL BUILDING with parking for doctors and patients. Stately suites or individual offices. Magnificent fireplaces, chandeliers, fresco ceilings, parquet floors. Elevator. Water-side Beacon Street near Gloucester. Secretarial, telephone services can be shared. Available immediately. Please call KEnmore 6-1364. B58-13-tf

COLONIC IRRIGATIONS, massage, diathermy. Beatrice M. Woods, 511 Beacon Street, Boston, CO 6-8722. B80-16-tf

FOR RENT — Offices for a physician or dentist. Excellent location. Reasonable rent. Several large rooms. 83 Maple Street, Springfield, Massachusetts. REpublic 4-4111. B27-6-tf

OFFICE FURNITURE—New—Used—Refinished. Bought and sold. Desk Clearing House, 115 Broad Street, Boston. HU 2-1318. B72-22-tf

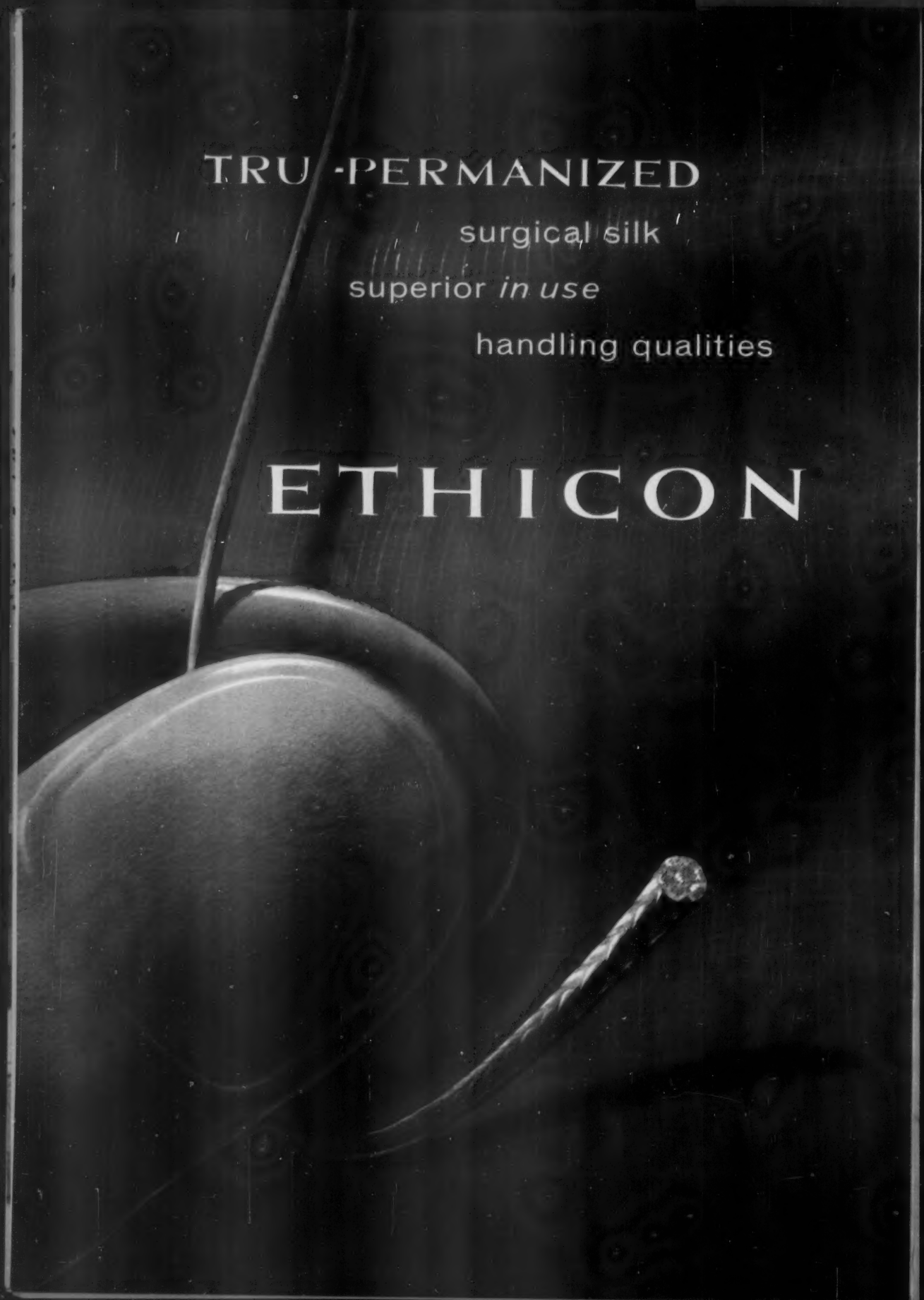
(Additional advertisements on page xxxvi)



setting new standards

ETHICON®

sutures


TRU-PERMANIZED
surgical silk
superior *in use*
handling qualities
ETHICON

LIVITAMIN® with IRON
each fluidounce contains:

Iron peptonized..... 420 mg.
(Equiv. in elemental iron to 70 mg.)
Manganese citrate, soluble..... 158 mg.
Thiamine hydrochloride..... 10 mg.
Riboflavin..... 10 mg.
Vitamin B_{12} (crystalline)..... 20 mcg.
Niacinamide..... 50 mg.
Pyridoxine hydrochloride..... 1 mg.
Pantothenic acid..... 5 mg.
Liver fraction 1..... 2 Gm.
Rice bran extract..... 1 Gm.
Inositol..... 30 mg.
Choline..... 60 mg.

. . . the reconstructive iron tonic of wide application . . .

LIVITAMIN®

WITH IRON

In debilitation, syndrome therapy instead of symptom treatment is required. Livitamin (Massengill) provides comprehensive therapy and adequate nutritional support. The appetite improves, as does the blood picture . . . improved anabolism and better digestion produce a significant syndrome reversal.

LIVITAMIN® CAPSULES with INTRINSIC FACTOR
each capsule contains:

Desiccated liver..... 450 mg.
Ferrous sulfate..... 130 mg.
(Equiv. to 25 mg. of elemental iron)
Thiamine hydrochloride..... 3 mg.
Riboflavin..... 3 mg.
Niacinamide..... 10 mg.
Vitamin B_{12}..... 5 mcg.
Pyridoxine hydrochloride..... 0.5 mg.
Calcium pantothenate..... 2 mg.
Folic acid..... 1 mg.
Intrinsic factor USP..... 1/6 Unit

. . . in pernicious anemia and geriatrics . . .

LIVITAMIN®

CAPSULES WITH INTRINSIC FACTOR

Intrinsic factor is essential to provide full utilization of antianemic and nutritional factors in P. A. and many Geriatric patients. Livitamin Capsules with Intrinsic Factor (Massengill) contain intrinsic factor, U.S.P., iron and the B-complex vitamins. This integrated medication provides an optimal response in these difficult patients.

THE S. E. MASSENGILL COMPANY
BRISTOL, TENNESSEE

Founded 1879

RING SANATORIUM

EIGHT MILES FROM BOSTON

For the study, care and treatment of emotional, mental, personality and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring psychiatric, medical, or neurological supervision.

Full resident and associate staff. Courtesy privileges to qualified physicians.

BENJAMIN SIMON, M.D.
Director

CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights
Massachusetts
Mission 8-0081

Woodside Cottages

FRAMINGHAM, MASS.

A sanitarium specially adapted for nervous and convalescent patients who need rest and upbuilding in normal surroundings.
No committed mental cases.

ARTHUR H. WARD, M.D., *Medical Director*

PERKINS SCHOOL

LANCASTER, MASS.

Devoted to the scientific understanding and education of children of retarded development. Five homelike and attractive buildings surrounded by 85 acres of campus and gardens.

FRANKLIN H. PERKINS, M.D.

WESTWOOD LODGE

Incorporated

WESTWOOD, MASSACHUSETTS

Telephone NO 7-0168

A modern sanitarium for the treatment and care of mental and nervous disorders by a specialized staff experienced in psychotherapy, electroshock therapy and its modifications (electrocoma with or without electroshock) and other psychiatric treatments. Latest techniques used in the treatment of alcoholism and drug addiction. Excellent facilities for the care of senile and aged patients.

Homelike atmosphere in quiet country surroundings near Boston. Tennis court and occupational-therapy building on the grounds.

Outpatient department for referred cases only.

MARTHA BRUNNER-ORNE, M.D., *Superintendent*

SIDNEY M. BUNKER, M.D., *Psychiatrist*

WILLIAM J. HAMMOND, *Administrator*

Wiswall Sanatorium

203 GROVE ST., WELLESLEY, MASS.

For the care of mild mental and nervous patients in country surroundings. Small grouping allows a homelike atmosphere and personal contact.

E. H. WISWALL, M.D., *Superintendent*
HALE POWERS, M.D., *Medical Director*
Tel. WE 5-0261

STORROW HOUSE

(Former Storrow Estate at Lincoln, Mass.)
STAFFED AND OPERATED BY THE
MASSACHUSETTS GENERAL HOSPITAL

For nonpsychiatric ambulatory and semi-ambulatory patients needing rest or convalescent facilities.

CHARGES: $7.00 to $10.00 per day

Transportation for visits to physician's office provided. For information, call CLearwater 9-8343 or Massachusetts General Hospital Admitting Office LA 3-8200.

BALDPATE, Inc.

GEORGETOWN, MASSACHUSETTS

Telephone GEO 2131

LOCATED IN THE HILLS OF ESSEX COUNTY
30 miles north of Boston

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment; electric shock treatments, subcoma and deep coma insulin therapy when indicated; sleep treatment for withdrawal of narcotics.

Occupation under a trained therapist, diversions and outdoor activities.

G. M. SCHLOMER, M.D.
Medical Director

GLENSIDE

JAMAICA PLAIN, BOSTON, MASS.

A small, attractively located sanitarium for nervous, mild mental or chronic illnesses.

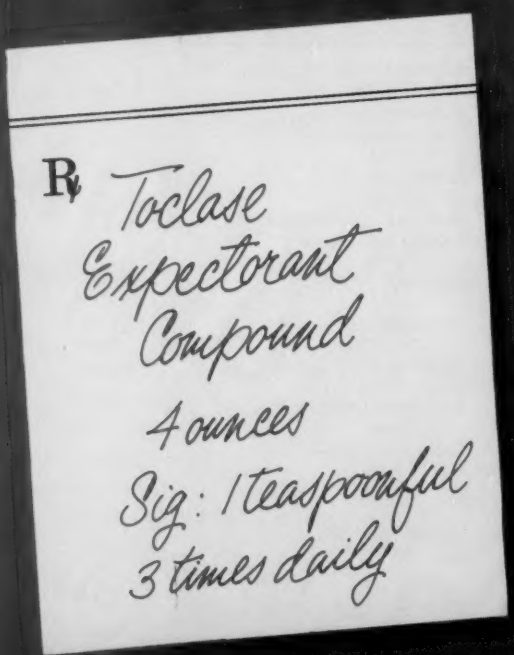
6 Parley Vale — Tel. JA 4-0044

DAVID MEMORIAL NURSING HOME

BROOKLINE 46, MASS.
S. D. COHEN, R.N., *Supt.*
Convalescents — Invalid-Elderly
Accepted by Blue Cross - Blue Shield
Prolonged Illness Program

61 Park Street — BE 2-3530

When you write...



Lederle

FOLBESYN*

Vitamins *Lederle*

A well-balanced, high-potency vitamin formula containing B-Complex and C

FOLBESYN provides B-Complex factors (including folic acid and B_{12}) and ascorbic acid in a well balanced formula. It does not contain excessive amounts of any one factor.

FOLBESYN Parenteral may be administered intramuscularly, or it may be added to various hospital intravenous solutions. It is useful for preoperative and postoperative treatment and during convalescence.

Dosage: 2 cc. daily. Each 2 cc. provides:

Thiamine HCl (B_1)	10 mg.
Sodium Pantothenate	10 mg.
Niacinamide	50 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Ascorbic Acid (C)	300 mg.
Vitamin B_{12}	15 micrograms
Folic Acid	3 mg.

FOLBESYN is also available in tablet form, ideal for supplementing the parenteral dose.

LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY Pearl River, New York

*REG. U.S. PAT. OFF.

you get... specific control of the hyperactive cough reflex—without undesirable opiate side effects

with new, non-narcotic, non-opiate

TOCLASE

Brand of carbetapentane

Available as: TOCLASE EXPECTORANT COMPOUND (sugar free, cherry flavored, amber color) bottles of 1 pint; TOCLASE SYRUP (cherry flavored, red color) bottles of 1 pint; TOCLASE TABLETS 25 mg., bottles of 25.

Pfizer PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

No single

provides

advantages

of the

REMEMBER: ALL SULFAS ARE NOT TRIPLE SULFAS!

sulfa the Triple Sulfas

- highest potency
- wide spectrum
- minimal side effects
- highest blood, plasma, and tissue levels
- safety
- economy

In every important way, judged by any test, the Council-accepted Triple Sulfas are still unexcelled among sulfa drugs. Constant use for many years has thoroughly proved their great worth. It is not surprising, then, that most leading pharmaceutical manufacturers offer the Triple Sulfas under their own brand names in a variety of forms, both alone and combined with other therapeutic agents.

These preparations are drugs of choice in many systemic, gastrointestinal, and urinary infections. Next time you find a sulfa drug is indicated, prescribe one of these effective preparations. For details, *ask any medical representative about the Triple Sulfa products his company offers.*

SULFADIAZINE **SULFAMERAZINE** **SULFAMETHAZINE** Meth-Dia-Mer Sulfonamides

Cyanamid Fine Chemicals

AMERICAN Cyanamid COMPANY

FINE CHEMICALS DIVISION

30 ROCKEFELLER PLAZA, NEW YORK 20, N. Y.

FOR PRENATAL SUPPLEMENTATION

YOU CAN CHOOSE BETWEEN THESE 2 EASY-TO-TAKE FORMULAS

alike...

yet different!

NEW

Natalins-PF*

Mead *phosphorus-free vitamin-mineral capsules

Natalins

Mead prenatal vitamin-mineral capsules

One Natalins–PF capsule t.i.d. or 1 Natalins capsule t.i.d. supplies vitamin A 6000 units; vitamin D 600 units; ascorbic acid 100 mg.; thiamine 3 mg.; riboflavin 4.5 mg.; niacinamide 30 mg.; pyridoxine HCl 3 mg.; calcium pantothenate 3 mg.; folic acid 1 mg.; vitamin B_{12} (crystalline) 1 mcg.; iron (from ferrous sulfate) 22 mg.

Here's the difference

One Natalins–PF capsule t.i.d. supplies calcium carbonate to provide 450 mg. of phosphorus-free calcium. One Natalins capsule t.i.d. supplies veal bone ash to provide calcium 375 mg., and phosphorus 188 mg.

both alike
in patient acceptability

small size...
easy to swallow

small dosage...
one capsule t.i.d.

economical, too

MEAD

SYMBOL OF SERVICE TO THE PHYSICIAN

MEAD JOHNSON & COMPANY, EVANSVILLE, INDIANA, U. S. A.